Deep vein thrombosis and pulmonary emboli in neurosurgical patients: a review

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This review examines the incidence, natural history, diagnosis, prophylaxis, and management of deep vein thrombosis (DVT) and pulmonary embolism (PE) in neurosurgical patients. Recent studies estimate the incidence of postoperative DVT detected by fibrinogen scanning in neurosurgical patients to be 29% to 43%. Specific factors that enhance the risk of venous thromboembolism include previous DVT, surgery, immobilization, advanced age, obesity, limb weakness, heart failure, and lower extremity trauma. Clinical diagnosis of venous thromboembolism is unreliable but can be augmented by noninvasive screening tests such as iodine-125-fibrinogen scanning, Doppler ultrasonography, and impedance plethysmography. As prophylactic measures, mini-dose heparin and external pneumatic compression of the legs have decreased the incidence of DVT in clinical studies of neurosurgical patients. However, no prophylactic measure has been convincingly shown to prevent PE in neurosurgical patients. Thrombi involving the popliteal, deep femoral, and iliac veins appear most likely to cause significant PE. Anticoagulation therapy constitutes standard management of DVT and PE; however, in neurosurgical patients the potential for precipitating intracranial or intraspinal hemorrhage may necessitate vena caval interruption. This appears to be an effective alternative to anticoagulation.

KEY WORDS • deep vein thrombosis • mini-dose heparin anticoagulation • pulmonary embolism • vena caval interruption • external pneumatic compression • impedance plethysmography

IN 1934, Homans described the relationship between deep vein thrombosis (DVT) in the leg and pulmonary embolism (PE). Since then, thromboembolism has become well recognized as a major public health problem. It is estimated that pulmonary embolism contributes to death in approximately 150,000 cases each year. Deep vein thrombosis in the leg is clinically recognized in about 250,000 cases annually, and there are about 7,000,000 patients with post-phlebitic sequelae in the United States. Although both DVT and PE occur regularly in neurosurgery, there is little organized information about these conditions that is readily available to neurosurgeons. The goal of this review is to present data on incidence, natural history, diagnosis, prophylaxis, and management for both DVT and PE.

Deep Vein Thrombosis

Incidence and Risk Factors

Recent reviews have estimated the frequency of postoperative venous thrombosis in the calf of neurosurgical patients to be 29% to 43%, as measured by the radio-labeled fibrinogen technique. Using the same technique, the incidence of venous thrombosis was found to be 30% in general surgical, 54% in orthopedic, and 50% in urological patients. The incidence of clinically evident DVT is considerably lower than this, creating one of the difficulties in management (see Diagnosis section below).

Extensive epidemiological study of thromboembolism has identified several factors that enhance the risk of developing DVT as defined by iodine-125 (125I)-fibrinogen uptake. They include: surgery, patient's age, heart failure, previous thromboembolism, direct trauma to the leg, varicose veins, oral contraceptives, obesity, Gram-negative sepsis, malignancy, inflammatory bowel disorder, and limb weakness. There is no difference in the frequency of venous thromboembolism between sexes.

Surgery. Surgery, especially a lengthy procedure, has been observed to increase the risk of developing DVT. Valladares and Hankinson reported an incidence of 50% for DVT detected by 125I-fibrinogen scanning in neurosurgical patients whose surgery lasted more than...
4 hours, compared to 24% in patients undergoing shorter procedures. Surgery causes changes in coagulation and platelet function that may favor thrombus formation. The period of immobility during surgery has also been shown to produce stasis in the venous sinuses of the calf. If this leads to vessel wall hypoxia in the vein cusps, as suggested by Hamer, et al., transient hypercoagulability fulfills Virchow’s scenario of stasis, vessel wall injury, and altered coagulation to initiate a thrombus in surgical patients.

**Patient’s Age.** Increased incidence of DVT with increasing age, especially in patients over 60 years old, has been noted in both autopsy and clinical studies. The reason is unknown, and there is no evidence that changes of aging in veins correlate with DVT.

**Heart Failure.** Both acute and chronic heart failure are associated with a two- to threefold increase in the incidence of DVT. Pulmonary emboli in cardiac patients do not come from mural thrombi, which account for only about 10% of PE in such patients; the vast majority of PE originates in the proximal venous system of the lower extremities.

**Previous Thromboembolism.** A history of thromboembolism has been noted to increase the risk of DVT two- to threefold in general surgical patients.

**Direct Trauma to the Leg.** Accidental trauma, especially to the lower extremity or hip, leads to increased risk of developing DVT. In this setting, the thigh may be the primary site of thrombi without antecedent calf vein thrombosis.

**Varicose Veins.** Varicose veins have been reported to increase the incidence of thrombosis in the legs as detected by 125I-fibrinogen scanning. The fibrinogen technique, however, does not distinguish between deep and superficial vein thrombosis, and is therefore an unreliable indicator of DVT. There is no evidence that superficial vein thrombosis increases the risk of DVT.

**Oral Contraceptives.** In a retrospective study of 175 patients from 43 hospitals, Sartwell, et al., found a greater than fourfold increase in the incidence of thromboembolism in women using oral contraceptives. There is also evidence that oral contraceptives are associated with increased risk of postoperative thromboembolism when taken in the month prior to surgery. In view of this, Coon has suggested discontinuation of contraceptives 1 month preoperatively.

**Other Risk Factors.** Obesity, Gram-negative sepsis, malignancy (especially of the pancreas), pregnancy, and inflammatory bowel disease are also associated with an increased risk for thromboembolism. Brisman and Mendell have reported an increased incidence of thromboembolic complications in patients with suprasellar tumors when compared with other brain tumors. They found thromboembolism in 33% of autopsied suprasellar tumors versus 6.7% of brain tumors in other locations. In a larger series of 100 neurosurgical patients, no significant difference in incidence was noted between craniotomy (both supra- and infratentorial) and laminectomy patients.

Limb weakness is a well known risk factor. Warlow, et al., studied 30 patients with recent stroke using radiolabeled fibrinogen scanning and found that DVT had developed within 10 days in 60% of paralyzed versus 7% of nonparalyzed legs.

**Natural History**

Virchow’s postulated requirements for thromboembolism included stasis and vessel wall injury. Venous thrombi appear to originate predominantly in regions of stasis such as the venous sinuses in the soleus and gastrocnemius muscles. It may be that stasis itself accounts for vessel wall injury since the endothelium covering valve cusps is dependent upon luminal blood for oxygen supply. Hamer, et al., have demonstrated hypoxia and early thrombosis formation in leg vein sinuses during conditions of stasis.

There are two important sequelae of leg vein thrombosis: post-phlebitic syndrome and PE. The relationship between DVT and PE is considered in the section on PE below.

The post-phlebitic syndrome is characterized by leg pain, edema, pigmentation, and ulceration. It can be debilitating and is seen with disturbing frequency following DVT of the leg. One or more symptoms of post-phlebitic syndrome occur within 3 years in 50% of patients clinically diagnosed as having DVT. In patients with DVT diagnosed by radiolabeled fibrinogen scanning, Browse and Clemenson found that approximately 25% complained of pain and swelling after 2 years. In a prospective analysis of 61 patients after acute, clinically evident DVT, Strandness, et al., found pain and swelling in 61% of cases, pigmentation in 15%, and ulceration in 5%. They emphasized the importance of functional deep venous valves and found a high correlation between occlusion or incompetence of the distal deep venous system (as determined by Doppler ultrasound) and the development of post-phlebitic sequelae.

Support hose is commonly prescribed for patients after acute DVT in an attempt to prevent post-phlebitic changes. Moderate exercise and elevation of the legs while at rest are also usually recommended.

**Diagnosis and Screening of DVT**

Clinical diagnosis of thromboembolism is unreliable and inaccurate. In neurosurgical patients with venogram-documented DVT, only 17% were symptomatic and just 10% had physical stigmata, such as calf tenderness, or edema. The difficulty of clinical diagnosis has been aided, however, by the development of several modalities that enhance overall diagnostic accuracy.

Ascending venography is the definitive test for the diagnosis of DVT. It is, however, a relatively invasive study. It may not show thrombi in the setting of PE either because all clots have embolized to the lung or...
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because the source of embolism is elsewhere. It has a 1% incidence of thrombophlebitis associated with it. Moreover, because of the inaccuracy of physical examination in selecting patients for venographic study and because venography does not lend itself to repeated examination, less invasive screening tests have been developed to detect DVT.

Radiolabeled fibrinogen scanning with $^{125}$I detects the incorporation of circulating labeled fibrinogen into a developing thrombus. A patient may be scanned as often as required for 5 to 7 days after a single intravenous injection of 100 $\mu$Ci of $^{125}$I-labeled fibrinogen. Readings are taken over the legs and measured as a percentage of activity over the heart. In a prospective study of 150 orthopedic patients, this method accurately predicted the presence or absence of leg DVT 70% of the time, with a true positive rate of 76% and true negative rate of 76% when compared to venography.

High background radiation from the femoral artery and bladder makes this technique inaccurate for detection of clots originating in the pelvis and upper thigh. Additional limitations, such as poor prediction of the extent of thrombosis and occasional delay before yielding a positive study (as fibrinogen is incorporated into a slowly growing thrombus), make this method more useful as a noninvasive monitor of patients at risk than as a diagnostic tool.

Impedance plethysmography and Doppler ultrasonography detect thrombosis best in proximal veins, but are less sensitive to calf vein thrombosis. The former detects changes in electrical resistance caused by flow of blood into calf veins associated with respiration or pneumatic thigh cuff occlusion. A Doppler ultrasound velocity detector senses blood flow by analyzing the shift in frequency caused in a continuous wave signal transmitted by moving red blood cells. Manual compression of the extremity produces a pulse wave that propagates up and down the venous system. Alterations in the resultant wave are used to identify the presence of intraluminal venous obstruction. Sigel, et al., found Doppler ultrasound to have 76% sensitivity and 68% specificity for detection of DVT compared to venography. Test accuracy, however, depends heavily on the skill of the examiner and can be low, particularly in calf and pelvic veins. These tests can be used alone, but are frequently used to supplement radiolabeled fibrinogen scanning data.

Thermography has also been used with early success in detecting raised baseline temperature and delayed cooling of extremities with DVT. Cooke and Pilcher used a thermographic scanning camera to predict DVT in 51 of 53 asymptomatic patients with venogram-documented thrombi. The technique, however, does not distinguish between proximal and distal thrombi.

**Prophylaxis for Deep Vein Thrombosis**

The ideal way to manage thromboembolism is to prevent it. Salzman and Davies have suggested that, while the per patient dollar cost of prophylaxis is greater than treating thromboembolic events, the additional expense is justified by the lives saved.

Simple methods, such as elevation of the legs during surgery and the use of elastic stockings, are popular and easily employed. Lewis and co-workers found that the Trendelenburg position favored good venous return during surgery. Unfortunately, however, recent evidence suggests that elastic stockings are ineffective in preventing DVT. Rosengarten, et al., and Lewis, et al., found no decrease in postoperative DVT using compression stockings and leg wrapping, respectively.

In 1950, de Takats noted that less heparin was required to prevent clotting than to treat a formed clot, and suggested mini-dose heparin (5000 U subcutaneously twice daily) as a prophylactic measure. Heparin in this dosage inhibits Factor X activation (thereby interrupting both intrinsic and extrinsic clotting mechanisms), but causes only minor changes in the conventional measurements of clotting capacity.

In a group of 1660 general, orthopedic, urological, and gynecological surgical patients who received postoperative mini-dose heparin, 5000 U three times a day, 166 developed wound hematomas or required reoperation because of bleeding problems. Limited series analyzing results obtained with mini-dose heparin in neurosurgical patients, however, have noted it to be both safe and effective in reducing the incidence of DVT. Barnett, et al., reported no intraoperative complications, but reported two wound hematomas and four wound seromas postoperatively that required aspiration or reoperation. These six patients were part of a group of 150 given subcutaneous heparin, 5000 U, preoperatively and then twice a day for as long as they were confined to bed. It was concluded that mini-dose heparin could be used safely without an increased rate of postoperative bleeding. Cerrato and colleagues randomly allotted 50 neurosurgical patients to a control group and 50 to a group that received subcutaneous heparin, 5000 U, preoperatively and then every 8 hours for at least 7 days thereafter. The incidence of DVT detected by radiolabeled fibrinogen was 43% in the control group and 6% in the heparin-treated group. A recent review suggests that mini-dose heparin prophylaxis should be considered in neurosurgical patients over the age of 40 years and in those under 40 years old with two or more recognized risk factors.

Dextran is thought to interfere with platelet function by inhibiting Factor VIII and the von Willebrand factor, allowing fibrinolytic activity to dissolve thrombi. It has been found to decrease fatal PE but not DVT in general surgical patients. In a study involving 1875 surgical patients, allergic reactions were seen in approximately 1% of cases and wound hematomas and other significant bleeding occurred at a rate of 6%. Powers and Edwards have cautioned against the use of dextran in patients with blood-brain barrier defects. They warn that cerebral edema can be exacerbated by leakage of dextran into the interstitial space.

External pneumatic compression (EPC) of the legs...
was superior to low-dose heparin in preventing DVT in urological patients studied by Coe, et al. The mechanism of this prophylactic measure is likely more complex than just the mechanical induction of pulsatile flow. Intermittent pneumatic compression of the arms of surgical patients decreased the incidence of DVT in the legs, and was found to prevent the usual decrease in fibrinolytic activity seen postoperatively. This finding supports the idea that release of fibrinolytic activators may play a role in its prophylactic action.

Two prospective randomized series have shown EPC to be effective in decreasing the incidence of DVT in neurosurgical patients. Skillman, et al., randomly allotted 95 neurosurgical patients into a control group and a group given EPC. Twelve patients (25%) of the control group and four (8.5%) of the EPC group developed DVT as documented by radiolabeled fibrinogen scanning. In 161 postoperative neurosurgical patients, Turpie, et al., found DVT in 18.4% of controls and 1.9% of patients given EPC for 5 days; they also used the radiolabeled fibrinogen technique.

Aspirin and Coumadin (warfarin) have decreased the incidence of DVT in some orthopedic patients, but neither has been studied in neurosurgical series.

Management of Deep Vein Thrombosis

The main goal of DVT therapy is to prevent PE. Thrombi at any level can cause PE, but most investigators agree that thrombi in the thigh are the most threatening. When thrombi remain confined to the tibial veins, conservative management including bed rest, leg elevation, and heat application can be employed. This should be accompanied by regular screening surveillance to detect proximal extension into the popliteal and iliofemoral segments.

Standard management of proximal DVT includes anticoagulation with heparin and warfarin. While there is early indication that prophylactic mini-dose heparin may be used in postoperative neurosurgical patients, there has been no evaluation of the safety of full anticoagulation treatment. Furthermore, hemorrhage during heparin therapy can appear unpredictably in spite of close laboratory monitoring and has been reported with particular frequency in elderly women. One author has recommended waiting at least 5 days after craniotomy before proceeding with anticoagulation therapy.

If anticoagulation is contraindicated, such as in patients with intracranial hemorrhage or vascular tumors, methods to prevent PE by interruption of the inferior vena cava (IVC) can be employed. Initially, ligation of the IVC was utilized; however, acute total occlusion of the IVC was associated with a mortality rate of 13%, the threat of significant decrease in venous return resulting in hypotension, exacerbation of venous stasis, and the chance of PE in spite of the procedure. Problems such as these led to the development of alternative methods of interruption. Suture plication of the IVC was utilized until it was discovered that the channels between sutures can dilate and allow passage of thrombus.

Adams and DeWeese devised a plastic clip that is applied transabdominally and partitions the IVC into four or five channels, trapping emboli larger than 3 mm. This device has been used in a large number of patients. It has a patency rate of 85% at 6 months and a 4% incidence of recurrent PE after clipping. A significant increase in leg swelling after clipping has been noted in 21% of patients. Swelling can be seen in the nonphlebitic leg as well as the one with previously diagnosed DVT, and can be quite debilitating. While swelling persisted in 24% of the series reported by Donaldson, et al., no patients who underwent clipping had more severe sequelae, such as stasis or ulceration.

Two methods for transvenous placement of a device to prevent PE have been studied extensively: the Mobin-Uddin umbrella and the Kim-Ray Greenfield filter. Both are usually inserted via the internal jugular vein, although the Greenfield filter may be introduced transfemorally. The rate of PE after the procedure has been noted to be 2% to 3% for the Greenfield filter and 2.5% to 12% with the Mobin-Uddin umbrella. In one series, leg edema occurred in 38% of patients after placement of the Greenfield device and in 75% of cases with the Mobin-Uddin umbrella in place. Perforation of the vena cava has been reported with both devices.

Unilateral femoral vein ligation has only recently returned to the surgical armamentarium. Bilateral interruption used to be necessary because diagnostic methods to exclude the presence of thrombus in the unaffected extremity were unavailable. Most surgeons recommend anticoagulation therapy after such a procedure, perhaps limiting its usefulness in neurosurgical patients.

Pulmonary Embolism

Incidence, Risk Factors, and Natural History

Pulmonary embolism is the most devastating sequela to DVT, and remains a major concern to the neurosurgeon. The mortality rate from a single PE is approximately 20%, and increases with any subsequent episode. Pulmonary embolism is a frequent cause of death in hospitalized patients, in one series occurring in 9% of autopsied patients who died postoperatively. Among neurosurgical patients, Wetzel, et al., found that 3% of deaths were from PE.

Most venous thrombi begin in the deep veins of the calf: approximately 20% will propagate proximally into the popliteal, femoral, or iliac veins. Pulmonary embolism can be caused by thrombi at any level but is more likely to be clinically significant in patients with proximal vein thrombosis. In a recent autopsy series, two-thirds of emboli described as contributing to death originated in the proximal iliofemoral veins. In another study, PE was caused by emboli from sites below the
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popliteal vein in 30% of cases, and from clots in the femoral vein in 66%. However, the variability in sequence is seen in a neurosurgical series in which 40% of clots detected by radiolabeled fibrinogen in the calf were noted to extend proximally, but no pulmonary emboli were documented or suspected.38

Diagnosis of Pulmonary Embolism

Pulmonary embolism is no more accurately diagnosed today than it was 20 years ago.17 A correct clinical diagnosis was made during life in only 25% of patients with massive embolism noted at autopsy, and only about one-third of patients with clinical signs suggesting PE have the diagnosis confirmed by pulmonary angiogram.18 Pulmonary angiography is the definitive technique for diagnosing PE. It is best used acutely, as the characteristic radiographic picture may be less evident after 48 hours.71 This test should be performed in any case in which there are strong reasons for suspicion, with the exceptions noted below.

The clinical diagnosis of PE is known to be even less accurate than of DVT.18 Pleuritic pain and dyspnea are the most frequent symptoms, but in fact are absent in 40% of cases with documented pulmonary emboli.24 The electrocardiogram (EKG) is a nonspecific aid in the diagnosis. Ventricular ectopia with QRS complex abnormalities on the EKG, such as left axis deviation, is most common, while the picture of acute cor pulmonale in present in only about 10% of PE cases.33 The classic combination of hypoxia and hypocarbia can aid diagnosis if present. In one series it was rare for patients with PE to have PaO₂ greater than 90 mm Hg.78 In another, PaCO₂ less than 30 mm Hg helped diagnose actual pulmonary embolus while PaO₂ was nonspecific.24 The triad of elevated lactic dehydrogenase (LDH) and elevated bilirubin with normal serum glutamic oxaloacetic transaminase (SGOT) levels is rare and nonspecific.78

A chest x-ray film may occasionally reveal a wedge-shaped infiltrate secondary to infarction, a pleural effusion, atelectasis, or an elevated diaphragm. However, a normal chest film does not exclude the diagnosis of PE.71,76 The ventilation-perfusion lung scan uses inhaled xenon-133 and injected radiolabeled denatured albumin particles. This study may reveal abnormalities in cases of pneumonia, tuberculosis, chronic obstructive pulmonary disease, asthma, pleural effusion, and pulmonary embolism. A normal prestudy chest x-ray film enhances the reliability of this technique. Studies are grouped into normal and high or low probabilities; a “high probability” study is said to indicate a 75% to 85% chance of PE; a “low probability” scan shows less characteristic defects and suggests a 10% to 25% chance of PE.33,56

In patients with suspected PE, initial studies should include EKG, arterial blood gas sampling, a chest x-ray film, and a ventilation-perfusion scan. If the chest x-ray film and scan are normal, PE is excluded with 95% confidence. If a scan suggests a high probability of PE, there is an 85% chance of actual PE. The decision then must be made whether to manage the patient on these data alone or proceed to pulmonary angiography. If the scan yields a low probability of PE and clinical suspicion is high, a positive venogram will increase the likelihood of PE and may in itself be an indication for anticoagulation or IVC interruption. If the venogram is normal and clinical suspicion remains high, a pulmonary angiogram should still be considered.

Prophylaxis for Pulmonary Embolism

Prevention of fatal PE is the ultimate goal of both prophylaxis and therapeutic efforts. Measures that are known to help prevent DVT may not influence development of PE and vice versa.

Mini-dose heparin was found to reduce significantly the incidence of fatal postoperative PE in a multicenter trial involving multiple surgical specialties conducted by Kakkar and associates.41 Heparin, 5000 U given subcutaneously 2 hours before operation and three times daily thereafter for 6 days, significantly reduced the incidence of autopsy-documented fatal PE from 0.7% among 2076 control patients to 0.09% of the treated group. The value of mini-dose heparin in the prevention of fatal PE has recently been challenged, however; it failed to prevent PE in a group of 100 general surgical patients compared to 100 control patients analyzed prospectively in the Groote Schuur Hospital Thromboembolism Study.28 It also failed to prevent PE in patients after hip surgery.87

Although current data suggest that EPC may be efficacious in decreasing the incidence of DVT in neurosurgical and other patients,72 there has been no study that has definitively evaluated the value of EPC in preventing PE. Conversely, 500 ml dextran given intravenously on induction of anesthesia and repeated at the conclusion of the procedure has been found to reduce the incidence of PE but not DVT45 in general surgical patients.

Surveillance in the form of routine screening for DVT can be an effective but expensive method of PE prophylaxis. Salzman and Davies44 found no deaths from PE among 1373 patients accumulated from nine studies where surveillance methods were used accompanied by any specific prophylactic measures such as mini-dose heparin or EPC.

Management of Pulmonary Embolism

Initial management of PE includes administration of oxygen to combat hypoxia and intravenous fluids, and occasionally vasopressors to maintain blood pressure. Anticoagulation therapy with intravenous heparin given initially as a bolus (5000 to 10,000 U) and subsequently as a continuous infusion (25 U/kg/hr) is the definitive therapeutic maneuver. Heparin is usually continued for 7 to 10 days, followed by long-term anticoagulation with warfarin. Oral anticoagulation
therapy can be initiated 48 hours after heparin is started to allow time for dose regulation. However, as discussed above, anticoagulation may be contraindicated in some neurosurgical patients, necessitating other forms of management.

Thrombolytic therapy has been used successfully to augment endogenous fibrinolysis in a number of thrombotic conditions. In patients with lower extremity DVT, streptokinase has been shown to produce rapid clot lysis and a lower incidence of venous valve damage, suggesting that post-phlebitic sequelae may be reduced by this agent.42 Urokinase and streptokinase can cause rapid clot lysis in PE also, and have been recommended for use in severely ill patients with life-threatening PE.79 Citing the 5% to 9% hemorrhage rate observed with the use of thrombolytic agents, however, a National Institutes of Health publication has recently cautioned against their use within 2 months of intracranial or intraspinal surgery.58

After sublethal PE has occurred, vena caval interruption (see above) can be used as a prophylactic measure to prevent further PE. Because of the potential for catastrophic hemorrhagic complications attendant to other therapeutic modalities, this is frequently the only form of therapy used in neurosurgical patients with PE.61

Conclusions

It is important to be familiar with DVT and PE in neurosurgical practice. These entities frequently occur in patients with otherwise good prognoses, and their management can be complicated by circumstances unique to neurosurgery. Factors that increase the potential for thromboembolism are well known, and include situations frequently encountered in neurosurgical patients such as previous surgery, prolonged immobility, advanced age, trauma to the leg, and weakness. Prophylactic measures such as mini-dose heparin and external pneumatic compression have been shown to decrease the incidence of DVT in neurosurgical patients. Prophylaxis against PE in neurosurgical patients has not been studied. Patients with multiple risk factors should be considered at risk for the development of thromboembolic complications, and should be considered for prophylactic therapy or surveillance for DVT. Venous thrombi involving the popliteal and iliofemoral systems are most likely to cause PE. Standard management of proximal DVT and PE involves anticoagulation therapy, but the potential of precipitating intracranial or intraspinal hemorrhage may necessitate vena caval interruption.

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