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Venous Thrombosis

Risk Factors, Management and Complications

Caroline H. Gutmann
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Preface

Thrombophilias can be defined as a group of inherited or acquired disorders that increase the risk of developing thrombosis. Venous thromboembolism (VT) is considered a multifactorial disease produced by a sum of risk factors that predispose to the thrombotic event. This predisposition includes genetic and acquired defects. Thrombosis can occur in any section of the venous system, but commonly manifests as deep vein thrombosis of the leg and pulmonary embolism. Major complications of venous thrombosis are a disabling post-thrombotic syndrome, pulmonary hypertension, and sudden death duo to a pulmonary embolism and therefore, it poses a burden on health economy. Venous thrombosis is a common clinical challenge for doctors of all disciplines, as it is a complex multicausal disease. This books discusses in further detail the many complications and risk factors caused by venous thrombosis.

Chapter 1 - Breast cancer is the most common malignancy in females, after skin cancer, with lifetime incidence of 12.4% and the second most common cause of cancer related deaths among women. Venous thromboembolic (VTE) events have been found to affect 0.16 to 2.3% of breast cancer patients and are associated with increased mortality. Nearly all breast cancer patients require mastectomy or lumpectomy as part of the treatment regimen and many of these patients also undergo reconstruction, either immediate or delayed. Risk factors associated with VTE include advanced cancer stage, prolonged operative time, inpatient hospitalization, immediate reconstruction, chronic medical comorbidities, venous catheterization, age, obesity, and tamoxifen or chemotherapy use. This chapter will focus on VTE complications that arise from surgical treatment, mastectomy, and breast reconstruction, in breast cancer patients. Identifying risk factors will help guide physicians to improved prevention practices and hopefully a standardized VTE prophylaxis protocol for breast cancer patients.

Chapter 2 - The clinical significance of isolated calf vein thrombosis (ICVT) is controversial. It has not been adequately studied and its diagnostic and management guidelines are not universally similar. The majority of ICVTs are asymptomatic, diagnosed on screening ultrasound duplex sonography and do not propagate above the knee. A smaller portion of ICVTs are symptomatic and may propagate this subgroup can cause significant morbidity and even mortality. Management of ICVT differs among physicians and institutions. Some therapeutically anticoagulate, whereas some advise chemical and/or mechanical prophylaxis. Some physicians advise close surveillance with repetitive duplex scanning. For patients that are at high risk for clot propagation short term theoretic anticoagulation is recommended.

Chapter 3 – The incidence of deep venous thrombosis (DVT) in the surgical population varies by type of patient and surgical procedure, contributing an unknown percentile of the overall estimated 250,000 DVTs annually.

Most DVTs are proximal and are found above the knee in the iliac, femoral, or popliteal veins. Those found below the knee, in any of the three groups of paired deep calf veins, are typically considered of less clinical significance. Upper extremity DVTs, in the axillary and subclavian veins, account for 5% of DVTs and are seen most often in the surgical patient associated with indwelling catheters or in patients with malignancy; 30% of these DVTs are estimated to lead to pulmonary embolism (PE). Risk factors for DVT include advanced age, malignancy, immobilization, trauma, oral contraceptives, hormone replacement, pregnancy, obesity, neurologic or cardiac disease, prolonged travel, and inflammatory states. A recent review of 1,485 spinal surgery patients found similar factors such as active malignancy, prior DVT or PE, estrogen replacement therapy, and renal disease to be significant on univariate analysis.

Interestingly, on multivariate analysis, estrogen replacement therapy and discharge to a rehabilitation facility had the strongest correlations as risk factors for DVT or PE.

A high index of suspicion is necessary for early diagnosis of this condition. Signs and symptoms include pain, edema usually of the calf or ankle, and warmth or erythema of the skin over the thrombosis. More than 50% of DVTs are asymptomatic and found solely on imaging. Duplex ultrasound imaging is highly sensitive and specific. Laboratory tests such as

D-dimer can be useful adjuncts in making the diagnosis of DVT, although this is not as sensitive or specific for the disease as duplex ultrasonography.

The goal of DVT treatment is to reduce the risk of PE, decrease extension of DVT, and prevent the almost 30% recurrence rate of an untreated DVT. Systemic anticoagulation is the mainstay of treatment in patients diagnosed with DVT and PE. Catheter directed pharmacologic thrombolysis is another option that is thought to preserve valve function. Inferior vena cava (IVC) filter placement is another aspect of DVT treatment.

Chapter 4 – Superficial thrombophlebitis is defined as inflammation and thrombosis of a vein near the skin's surface. Most studies underestimate the occurrence of superficial thormbophlebitis and although the greater or lesser saphenous veins are the most commonly affected veins, this disease can occur at any part of the body.

This condition is often associated with a long term intravenous (IV) catheter and is differentiated from septic thrombophlebitis by the absence of systemic signs of infection. Risk factors include recent venous catheterization, a history of previous superficial venous thrombosis, DVT or PE, recent surgery, trauma, pregnancy, high dose estrogen therapy, immobilization, malignancy, varicose veins, obesity, or intravenous drug abuse.

Superficial thrombophlebitis remains a clinical diagnosis. Symptoms include localized pain and warmth over the site and patients will present with tenderness to palpation, induration, and erythema over a palpable cord. It is noted that superficial thrombophlebitis coexists with DVT in up to 53% of cases and PE in up to 33% of cases. Superficial thrombo-phlebitis can progress rapidly to venous thromboembolism (VTE) in as much as 15% of cases.

Even though most times superficial thrombophlebitis will resolve on its own, it is not considered to be self limited and complications can occur. These include extension from a superficial vein to a deep vein, postphlebitic syndrome, chronic DVTs, suppurative thrombophlebilitis and septic thrombophlebitis.

The aim of treatment is to alleviate symptoms and prevent extension to deep veins. The mainstay of treatment consists of extremity elevation, warm compresses, and the use of non-steroidal anti-inflammatory drugs (NSAID). Most patients respond to this conservative management regime with symptom resolution or improvement in 7-10 days. There is some evidence that shows the use of subtherapeutic doses of low molecular weight heparin can help in prevention of extension of superficial thrombophlebitis to DVT but there are no large multicenter trials to support this and make it standard of care.

Chapter 5 – Thrombophilias can be defined as a group of inherited or acquired disorders that increase the risk of developing thrombosis. Venous thromboembolism (VT) is considered a multifactorial disease produced by a sum of risk factors that predispose to the thrombotic event. This predisposition includes genetic and acquired defects. VT is one of the major public health problems worldwide, contributing to an estimated >500,000 deaths in Europe each year, with a mortality rate of 10%. The risk of recurrence is about 6% per year, and post-thrombotic disease occurs within the next 5 years following a VT event in about 25% of patients. VT is a common multifactorial disease, with both established environmental and genetic risk factors.

The genetic basis of the VT is only partially known, and thrombophilia can only explain around 50% of the thrombotic events. Hence, the known risk factors, together with yet unknown alterations in any component of the haemostatic system, may allow us to further clarify the underlying mechanism of VT. The known genetic risk factors confer a poor relative VT risk, altogether can only explain about 5% of the VT heritability.

The identification of disease-associated VT genes suspected to be involved in the physiopathology of the disease could help to define its genetic determinants.

Moreover, the recent availability of high-throughput genotyping technologies and their application in the framework of genome-wide association studies (GWAS) have enabled the identification of novel susceptibility loci. From 1965 to 2013, 16 genes/loci have been robustly associated with the susceptibility to VT, most of them affecting the coagulation cascade. In addition to the well-known established susceptibility genes for VT: *F5*, *F2*, *FGG*, *PROC*, *PROS*, *SERPINC1*, and ABO blood group, new emerging susceptibility loci have arisen: *C4BPA/C4BPB*, *F11*, *G6P*, *HIVEP1*, *KNG1*, *STXBP5*, *TCN2*, *VWF*. However, independent case-control studies are needed to confirm the association with the disease for these emerging genes. This chapter summarizes the current information on the role of genetic risk factors for venous thrombosis.

Chapter 6 – The annual incidence of venous thrombosis varies from 40 per 100,000 to 250 per 100,000 in different populations. Thrombosis can occur in any section of the venous system, but commonly manifests as deep vein thrombosis of the leg and pulmonary embolism. Major complications of venous thrombosis are a disabling post-thrombotic syndrome, pulmonary hypertension, and sudden death duo to a pulmonary embolism and therefore, it poses a burden on health economy. Venous thrombosis is a common clinical challenge for doctors of all disciplines, as it is a complex multicausal disease.

Hereditary conditions account for ~60% of all the thrombosis incidents and a number of genetic risk factors have been identified so far. Acquired risk factors may contribute to variations within and between individuals. Diagnosis of thrombosis is not difficult with the development of imaging techniques. However, the most important steps for diagnosis are etiology analyzes and genetic tests, which are useful for assessments of duration of anticoagulant therapy and prevention for thrombosis.

Chapter 7 – Thrombotic diseases develop as the result of multiple interactions between non-genetic and genetic risk factors. The known atherogenic risk factors played an important role as predictors in the development of the thrombotic diseases in the present female case-control study. The most important non-genetic risk factors found among the female patients are: age, hypercholesterolemia, DM, use of oral contraception, obesity, and fibrinogen levels. Moreover, the stratified effect of some of these factors according to the age of the patients is relevant for clinical risk assessment. Associations between the risk of venous thrombosis (VT) and genetic polymorphisms have been established. Some of these polymorphisms are highly prevalent in Caucasians, but there is a significant geographic variation in their prevalence among different populations. The MTHFR C677T (rs1801133), are analyses in females with stroke, venous thrombosis and myocardial infarction in a case-control study. The C677TMTHFR mutation were detected in 149 patients and 113 controls (P=0,001). In the present study, the results showed that hypercholesterolemia, diabetes mellitus, and elevated levels of fibrinogen were present in the younger group as risks factors. Family history of thrombotic event (TE) was statistically significantly associated among the older female group. Median values of total fibrinogen were significantly higher in the cases compared with the control group. The small numbers of carriers of these risk factors require a note of caution on any conclusion. The present data suggest that MTHFR C677T genotype may be an important factor in the life of female patients at risk of developing TE or cardiovascular disease , p=0,001 between cases and controls groups . Folic acid supplementation of foods is necessary (and mandatory in Costa Rica) before and during women's reproductive phase. However, our data presented suggest that a case for efforts to ensure a good intake of this vitamin in the postmenopausal phase. Especially if the high prevalence of the MTHFR 677T homozygosity and of classic risk factors in the Costa Rican population are taken into account. Further studies with more patients are necessary for final conclusions for these interactions to be drawn.

Chapter 8 - Cerebral Venous thrombosis (CVT) accounts for nearly 1-2% of all strokes. Isolated cortical vein thrombosis (ICVT), a subtype of CVT, without sinus or great venous involvement is rare. It is often difficult to diagnose due to its varied clinical and imaging features. Hence, the available literature largely comprises of single center case series. The common presenting symptoms of ICVT are focal seizures, vaguely defined focal neurological deficits and visual disturbances. Headache and raised intracranial pressure are relatively uncommon. The underlying conditions which may predispose to ICVT are the same as described for typical CVT. However, rare associations of ICVT include lumbar puncture, Hodgkin's disease, nephrotic syndrome, vasculitis, inflammatory bowel disease and amyloid angiopathy. With a high index of suspicion, neuroimaging is essential for direct visualization of the thrombus, localized hemorrhage or small venous infarction. Visualization of thrombosed cortical vein (the cord sign) is observed infrequently. Management guidelines are not well established. However, initial anticoagulation with heparin followed by oral anticoagulation for 6-12 months remains the recommended guideline for treatment of ICVT. The prognosis is generally good with radiological resolution in most cases. In this review, we present the clinical spectra, etiopathogenesis, neuroimaging features and management options in ICVT patients.

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Chapter 1

Venous Thromboembolism in Oncologic and Reconstructive Breast Surgery

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Abstract

Breast cancer is the most common malignancy in females, after skin cancer, with lifetime incidence of 12.4% and the second most common cause of cancer related deaths among women. Venous thromboembolic (VTE) events have been found to affect 0.16 to 2.3% of breast cancer patients and are associated with increased mortality. Nearly all breast cancer patients require mastectomy or lumpectomy as part of the treatment regimen and many of these patients also undergo reconstruction, either immediate or delayed. Risk factors associated with VTE include advanced cancer stage, prolonged operative time, inpatient hospitalization, immediate reconstruction, chronic medical comorbidities, venous catheterization, age, obesity, and tamoxifen or chemotherapy use.

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This chapter will focus on VTE complications that arise from surgical treatment, mastectomy, and breast reconstruction, in breast cancer patients. Identifying risk factors will help guide physicians to improved prevention practices and hopefully a standardized VTE prophylaxis protocol for breast cancer patients.

Introduction

Venous thromboembolism (VTE) occurs rarely, but when unrecognized it can lead to significant morbidity and mortality. VTE encompasses both pulmonary embolism (PE) and deep vein thrombosis (DVT). Acute mortality from VTE is the result of embolic migration of a DVT into the pulmonary artery. In the general population, age-adjusted incidence of VTE is approximately 1 in 1000 people. [1] In cancer patients, this risk can be increased up to seven-fold, depending on the type of cancer. [1] VTE is preventable if high risk individuals are given prophylactic anti-coagulation.

Breast cancer is the most common form of cancer, aside from skin cancer, in women, occurring in 1 out of 8 women in the United States. [2] A review of the literature indicates that the risk of VTE in breast cancer ranges from 0.16 to 2.3%. Interestingly, while the incidence of VTE in breast cancer is lower than other forms of cancer, those who actually develop VTE in this setting have a very high mortality rate. [1,3] In fact, circulatory system disease, including VTE, is the second most common cause of death in breast cancer patients, following cancer itself. [4] Patients may also develop chronic symptoms from VTE, such as severe pain, edema, ulceration, post-phlebitic syndrome, and chronic thromboembolic pulmonary hypertension, leading to significant morbidity and decreased quality of life.

Until recently, the low incidence of VTE in breast cancer precluded researchers from understanding more about the disease. However, the development of regional and national registries and databases has given new insight into the disease process and risk factors for VTE in breast cancer patients. Because VTE is a preventable complication that has significant, life-threatening consequences, it is important to determine the risk factors and establish a standardized protocol for prophylaxis. Breast cancer treatments, including chemotherapy, hormonal therapy, radiotherapy, the placement of central venous catheters, and surgery itself greatly increase the likelihood of developing VTE. [5] To reduce this risk, some physicians have integrated routine use of pharmacologic anticoagulant prophylaxis, graded antithrombotic elastic compression stockings, and intermittent pneumatic compression devices into their practice. [5] Early ambulation and mechanical prophylaxis have shown to be best methods of VTE prevention for the majority of low risk breast cancer patients. [6]

This chapter will focus on VTE complications that arise from mastectomy and breast reconstruction in breast cancer patients. Identifying risk factors will help guide physicians to improved prevention practices and hopefully a standardized VTE prophylaxis protocol for breast cancer patients.

Venous Thromboembolism in Mastectomy Patients

The incidence of VTE in breast cancer patients ranges from 0.16-2.3%, [3,5] which is low compared to other malignancies; however, the high incidence of breast cancer translates to nearly 5,300 cases of VTE per year in U.S. breast cancer patients alone. VTE is a poor prognostic factor, correlating with worse overall survival and disease specific survival, in age, cancer type, stage, and surgical procedure matched patients. [7] In one series of 89 patients who underwent a modified radical mastectomy, two out of the five patients who developed a DVT also developed a PE, one of which died. [8] This increased mortality finding was also supported in a review of over 108,000 breast cancer patients that demonstrated a 2.3-fold increased risk of death over two years in breast cancer patients with VTE. [9] The American College of Chest Physicians (ACCP) publishes comprehensive evidence based clinical practice guidelines for antithrombotic therapy and prevention of thrombosis in medical and surgical patients. [10] The guidelines for general and abdominal surgery patients are summarized in Table 1; however, there are no evidence-based guidelines specifically for plastic and reconstructive surgery patients as there is a lack of randomized trials investigating VTE in these patients.[10] Clinically, despite well reported increased risk and associated mortality in breast cancer patients with VTE, a survey of over 600 reconstructive breast surgeons revealed only 25% of surgeons reported compliance with the ACCP guidelines on thromboprophylaxis. [11] Failure to meet the standard of care in VTE prevention has reinforced the need for all surgeons to assess whether VTE prophylaxis is indicated on a per patient basis. The Caprini risk assessment model (RAM), along with recent studies that improve our recognition of risk factors that confer greater risk of VTE in breast cancer patients, can help guide the decision to initiate VTE prophylaxis.

Table 1. Summary of ACCP recommendations for patients undergoing general or abdominal-pelvic surgeries. Recommendations compiled from American College of Chest Physicians recommendations. [10]

Level of risk for VTE	Recommendation
Very low risk (Caprini Score 0)	No specific pharmacologic or mechanical prophylaxis other than early ambulation
Low risk (Caprini score 1-2)	Mechanical prophylaxis, preferably IPC, over no prophylaxis
Moderate risk (Caprini score 3-4) who are NOT at high risk for major bleeding complication	LMWH, low dose UH, or mechanical prophylaxis, preferably IPC, over no prophylaxis
Moderate risk (Caprini score 3-4) who are at high risk for major bleeding complication or those in whom the consequences of bleeding are thought to be particularly severe	Mechanical prophylaxis, preferably IPC, over no prophylaxis
High risk (Caprini score ≥5) who are NOT at high risk for major bleeding complication	LMWH or low dose UH over no prophylaxis, suggest mechanical prophylaxis with elastic stockings or IPC should be added to pharmacologic prophylaxis
High risk undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications	Extended-duration pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis
High risk undergoing abdominal or pelvic surgery who are at high risk for major bleeding complication or those in whom the consequences of bleeding are thought to be particularly severe	Mechanical prophylaxis, preferably IPC, over no prophylaxis until risk of bleeding diminishes and pharmacologic prophylaxis may be initiated
High risk in whom both LMWH and UH are contraindicated or unavailable and who are not at high risk for major bleeding complications	Low-dose aspirin, fondaparinux, or mechanical prophylaxis, preferably IPC, over no prophylaxis

LMWH = low molecular weight heparin, UH = unfractionated heparin, IPC = intermittent pneumatic compression