ERABI EVIDENCE-BASED REVIEW of moderate to severe ACQUIRED BRAIN INJURY

Clinical Guidebook

9. Heterotopic Ossification and Venous Thromboembolism Post Acquired Brain Injury

Pavlina Faltynek MSc, Paul Phares MSc MD (c), Amber Harnett MSc, Robert Teasell MD FRCPC

Ontario Neurotrauma Foundation
Fondation ontarienne de neurotraumatologie

LAWSON HEALTH RESEARCH INSTITUTE

Western

St. JOSEPH's HEALTH CARE LONDON

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Heterotopic Ossification and Venous Thromboembolism Post Acquired Brain Injury

By the end of this chapter you should be able to:

- Identify the signs and symptoms of heterotopic ossification and venous thromboembolism
- Know the risk factors which can influence the development of either condition
- Know the appropriate screening assessments and outcome measures for each condition
- Understand the different treatment modalities available for each condition and the benefits and risks associated with each intervention

9.1 Introduction to Heterotopic Ossification

Heterotopic Ossification (HO) is a process whereby true mature lamellar bone forms ectopically within tissues where bone formation does not usually occur (Figure 9.1) (Watanabe & Sant, 2001a). Although HO can occur through a variety of mechanisms, its development specific to acquired brain injury (ABI) will be exclusively discussed in this chapter. The role of this chapter is to provide clinically relevant content for the management of HO following an ABI. The literature has been sourced from a variety of populations including those without ABI. If the content itself was deemed relevant to HO management following ABI, it was included. Although some areas of HO management have recently advanced, such as imaging and diagnosis, other areas such as risk factors and causes of HO are still poorly understood. Overall, HO is noted to be a manageable condition following ABI, given that appropriate interventions are initiated during critical periods. For scientific evidence supporting HO in ABI, please **Click here to see the online ERABI module on Heterotopic Ossification**

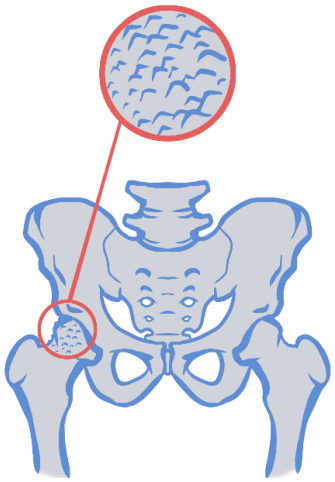

Figure 9.1 An illustration showing HO formation at the hip. The hip is the most common site of HO formation.

9.2 Clinical Presentation and Features of HO

9.2.1 Incidence of HO Following ABI

Q1. What is the clinically relevant incidence of HO? Name a risk factor.

1. 10-20%; Sustained fractures during initial trauma

The clinically relevant incidence of HO following an ABI has been reported to be 10-20%, although the overall incidences of HO has been reported as high as 77% (Dizdar et al., 2013; Garland et al., 1980; Rogers, 1988; Sarafis et al., 1999; Sazbon et al., 1981; Zychowicz, 2013). A recent survey of 48 institutes caring for those with severe ABI found that the incidence of HO following an ABI was 13.6%, with occurrence of HO not significantly differing between the etiologies of the injury (vascular vs traumatic) (Bargellesi et al., 2018). The incidence rate of HO following an ABI has been shown to be similar to rates observed in other conditions including spinal cord injury, total hip replacement, and polytrauma (Pape et al., 2001). However, the same study noted that those with an ABI had significantly higher rates of alkaline phosphatase one day and 6-weeks following trauma compared to other groups (Pape et al., 2001). Alkaline phosphatase is an enzyme found in high concentrations in bone tissue and may therefore be implicated in the formation of HO lesions. For those who developed HO following an ABI, HO was found to form specifically around those areas damaged during initial trauma (Pape et al., 2001). The hypothesis that HO is more likely to form around fractures sustained during the initial trauma has been supported by multiple studies (Garland et al., 1985; Garland & Rhoades, 1978; Pape et al., 2001). Currently-known risk factors for the development of HO following an ABI are presented in Table 9.1.

Table 9.1 Risk factors for HO following ABI

Risk Factors for the Development of HO following ABI (Bargellesi et al., 2018; Huang et al., 2018)
- Skeletal trauma - Diffuse axonal injury - Spasticity - Mechanical ventilation - Duration of coma - Tissue hypoxia - Spasticity - Prolonged immobilization - Injury severity

With respect to recurrence, a systematic review of 67 studies examining HO following traumatic brain injury (TBI) concluded that the risk of recurrence of Neurogenic HO (NHO) was not associated with an individual's cognitive status, the volume of HO formations following injury, or the timing of initial surgery (Almangour et al., 2016). The volume of bone formation is related to Brookers classification of HO (Class I-Class IV) (Brooker et al., 1973), where it was originally hypothesized that the more severe the HO formation the greater the risk of recurrence, but this has been found to be untrue. Another common risk factor of HO recurrence was thought to be the timing of initial HO surgery; however, multiple studies have found no link to support this (Almangour et al., 2016; Genet et al., 2012).

9.2.2 Clinical Presentation of Heterotopic Ossification

Q2. Describe the clinical features of heterotopic ossification (HO) post-ABI.

1. Clinical features of HO include a warm, swollen, and painful joint, associated with a decreased range of motion (Pape et al., 2004).

The onset of HO has been reported to vary between two and three weeks post injury (Watanabe & Sant, 2001a). More recently, clinical signs and symptoms have been reported to develop 3-12 weeks post injury

(Vanden Bossche & Vanderstraeten, 2005; Zychowicz, 2013). Several months after the initial trauma, patients with HO begin to experience restricted range of motion, pain, and in some cases, ankylosis (Banovac & Gonzalez, 1997; Garland et al., 1980).

Pape et al. (2004) have noted that clinical examination may reveal swollen, warm, and painful joints with decreased range of motion. Watanabe and Sant (2001b) have reported that the formation of HO generally precedes symptom onset with the earliest sign often being decreased range of motion in the involved joint. This can occur as early as two weeks post injury. Other findings include erythema, pain, palpation of a periarticular mass, and fever (Varghese, 1992). It can be difficult to rule out differential diagnoses (Citta-Pietrolungo et al., 1992; Garland et al., 1980; Garland, 1991). Understandably, the clinical picture may be confused with deep venous thrombosis (DVT), local infection, local trauma, or a fracture (Buschbacher, 1992; Jensen et al., 1987). It should be noted that although HO formation can begin early (2-3 weeks post injury), symptoms may not present until later (3-12 weeks post injury).

Q3. Which joints are most often involved in HO post ABI?

1. The joints most commonly affected are the hips, shoulders, and elbows. Rarely are the knees affected.

The most commonly affected joint is the hip (Figure 9.2), then the shoulder and elbow; rarely is the knee involved (Garland et al., 1980; Garland, 1991; van Kampen et al., 2011; Vanden Bossche & Vanderstraeten, 2005). Hip involvement can result in an 18-37% restriction of range of motion (Sarafis et al., 1999), with total ankylosis of the joint occurring in 5-16% of affected hips (Garland, 1991). Sarafis et al. (1999) have noted that the distribution of HO around the elbow occurs most commonly either anteriorly in the flexor muscles or posteriorly in the extensors. Of the joints affected by HO after brain injury, total ankylosis is most likely to occur in the elbow and it usually occurs posteriorly (Garland et al., 1980). The knee is the rarest site of HO following brain injury (Sarafis et al., 1999); however, when HO occurs at the knee, the most common site is the inferomedial aspect of the distal femur.

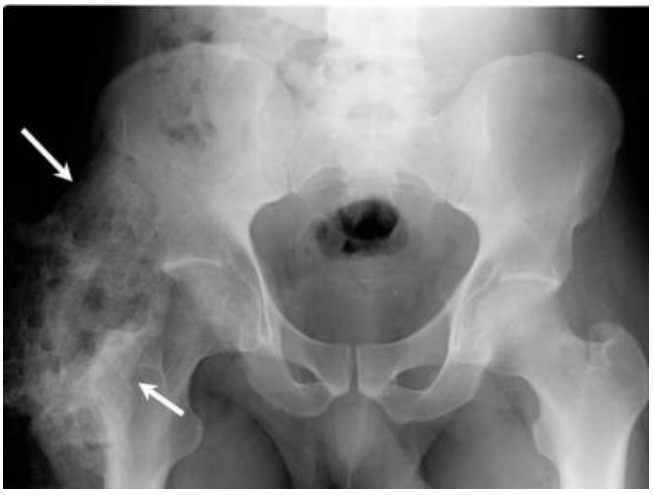

Figure 9.2 A radiograph showing the formation of HO at the hip; from LearningRadiology.com.

9.3 Outcome Measures and Clinical Assessments

Currently, the Clinical Practice Guideline for the Rehabilitation of Adults with Moderate to Severe TBI (2015) recommends regular physical screenings for possible indicators of HO, specifically for those with a severe TBI. Ultrasound may be performed first to serve as a quick, relatively inexpensive screening test which can differentiate HO from venous thromboembolism. A bone scan and CT scan are more involved but can provide more definitive diagnoses.

9.3.1 Ultrasonography

Over the last ten years ultrasound has proven to be helpful in the diagnosis of NHO (Falsetti et al., 2010; Lin et al., 2014a; Rosteius et al., 2017; Stefanidis et al., 2017). In a prospective study by Stefanidis et al. (2017) the efficacy of ultrasound as a potential diagnostic tool was evaluated in 310 individuals with ABI. The authors found that ultrasound interrogation was able to successfully detect HO in 21 of 310 patients (6.8%) (Stefanidis et al., 2017). Other studies support the efficacy of ultrasonography for the early detection of NHO showing that it has a sensitivity of 88.9% for detection of early signs of NHO at a mean time of 64.8 days post-injury (Falsetti et al., 2010; Rosteius et al., 2017).

Although final diagnosis is typically confirmed via x-ray or bone scan, ultrasonography has been shown to have specific benefits in the early detection over other methods. These benefits include portability for bedside examination, it is non-invasive, relatively low-risk, and cost effective (Falsetti et al., 2010; Rosteius et al., 2017).

9.3.2 Bone Scintigraphy or Bone Scans

In most cases a three-stage bone scan should be conducted (across three different time points) to best assess the extent of the HO lesion. If a comprehensive image of the formation is necessary, a single-photon emission-computed tomography (SPECT) procedure can be conducted to capture images of the formation from multiple angles and construct a 3-dimentional image of the bone over time.

9.3.3 Computed Tomography

Multiple studies have cited the benefits of CT use for confirming an HO diagnosis, determining the extent of HO formation, and the precise location of HO formation to guide surgical excision (Lin et al., 2014b; Salga et al., 2015; Zagarella et al., 2013). One study has reported CT scans as being particularly helpful in identifying the risk of recurrence of HO following surgical intervention (Lima et al., 2014). This compares the preoperative and postoperative CT with respect to osteoblastic activity. Overall, CT is a useful tool for the evaluation and monitoring of HO formation, specifically CT should be used when surgical intervention is being considered.

9.4 Criteria for Diagnosis

A diagnosis of HO can be made by a positive CT scan, bone scan, or even ultrasound. The diagnostic process typically starts with a clinical examination when HO is suspected; signs and symptoms indicating possible HO are restricted range of motion, swelling, warm, or painful joints. At this stage the presence of HO should be confirmed through a secondary assessment (positive scan result), with the assessment interpreted by an appropriately trained individual, such as a radiologist.

The Brooker classification model is commonly used to diagnose the extent of HO formation specifically to the hip (Brooker et al., 1973). Although the Brooker classification model has undergone multiple modifications, the original model is still widely used today to confirm the extent of HO formation (Figure 9.3) (Hug et al., 2015). In 2002, Della Valle et al., (2002) advanced the original Brooker classification model by defining bone island size, and spur separation, as well as a multitude of other variances which limited the reliability of the original system.

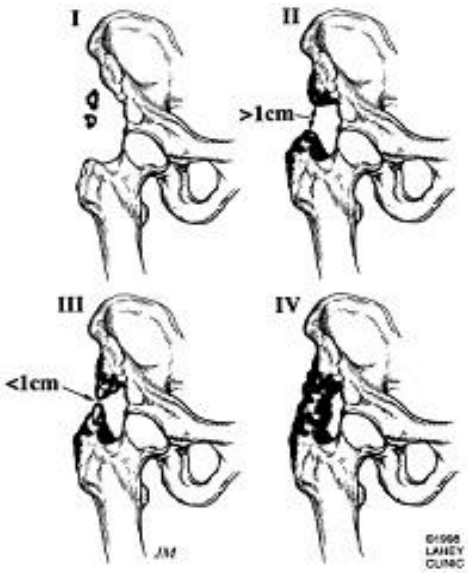

Figure 9.3 The original four Brooker classifications of HO formation at the hip. Taken from https://www.physio-pedia.com/Heterotopic_Ossification

Table 9.2 The Della Valle modified grading system of the original Brooker classification (Della Valle et al., 2002; Hug et al., 2015).

Grade	Description
Grade A	The presence of one, or greater than one, bone island less than 1 cm in length; or absence of HO.
Grade B	Presence of at least one island of bone, at least 1cm in length, combined with the presence of bone spurs which leave at least 1 cm between opposing bone surfaces. With bone spurs occurring at the pelvis or femur.
Grade C	Presence of bone spurs at the pelvis or femur with less than 1 cm between opposing bone surfaces combined with bone ankylosis.

9.5 Interventions for Heterotopic Ossification

Based on the challenges associated with diagnosing HO, coupled with the lack of understanding as to its genesis, recurrence rates of HO are typically high (Almangour et al., 2016). For this reason, it is important to determine which interventions are most successful for the treatment and management of HO following ABI. It should be noted that although an association between cognitive status and HO formation has been found in those with spinal cord injuries (SCI), no such association has been found in those with an ABI (Almangour et al., 2016).

9.5.1 Physiotherapy and Range of Motion Exercises

Early studies seemed to indicate that physiotherapy and range of motion exercises may have contributed to the development of HO (Chantraine & Minaire, 1981; Crawford et al., 1986). However, currently there is little evidence to support this. Pape et al. (2004) have noted that for HO, careful and judicious use of physiotherapy, involving assisted range of motion exercises and gentle stretching, are beneficial. However, it has been cautioned that care should be taken not to move the joint beyond its pain-free range of movement as this can exacerbate the condition (Evans, 1991; Pape et al., 2004).

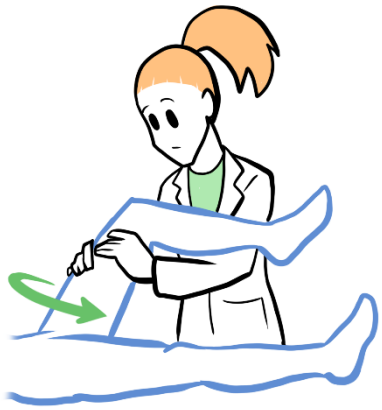

Figure 9.4 An example of a clinician assisted passive range of motion exercise for the hip.

In 1982 Garland et al., (1982) conducted a review of patients with TBI and HO who underwent forceful manipulation of their joints under anesthesia. Overall, 82% of joints experienced an increase in range of motion, with further gains being seen when coupled with rehabilitation. Garland and Varpetian (2003) also noted that patients with ABI frequently suffer from spasticity, intolerance to pain, and voluntary muscle guarding. As a result, anesthesia may be needed to help differentiate between spasticity and ankylosis and to allow for sufficient muscle relaxation to perform the joint manipulation (Garland & Varpetian, 2003). The Clinical Practice Guideline for the Rehabilitation of Adults with Moderate to Severe TBI recommend both the use of passive range of motion exercises and the option of forceful manipulation of joints under anesthesia if needed (INESSS-ONF, 2015). **Click here to see the INESSS-ONF Clinical Practice Guidelines for HO**

9.5.2 Shockwave and Radiotherapy

The aim of shockwave and radiation therapy is to disrupt the bone lesions through either vibration or radiation (Lee et al., 2016; Reznik et al., 2017). The goal of radiation therapy is to disrupt mesenchymal stem cell differentiation into osteoblasts during the early phases of HO (Balboni et al., 2006); by doing so, additional bone formation on a specific site should be arrested. Radiation therapy is also used after surgical interventions to decrease the HO recurrence. Shock wave/vibration therapy, in contrast, seeks to erode unwanted formations of bone (Reznik et al., 2017).

Extracorporeal shockwave therapy (ESWT) is an evolution from the technology used to treat kidney stones, which makes use of pressure waves (transient pressure oscillation) to disrupt the formation of neo-calcifications (Notarnicola & Moretti, 2012). Although the therapeutic mechanisms of ESWT are not fully understood, its benefit is believed to be at least in part to direct mechanical disintegration (Notarnicola & Moretti, 2012).

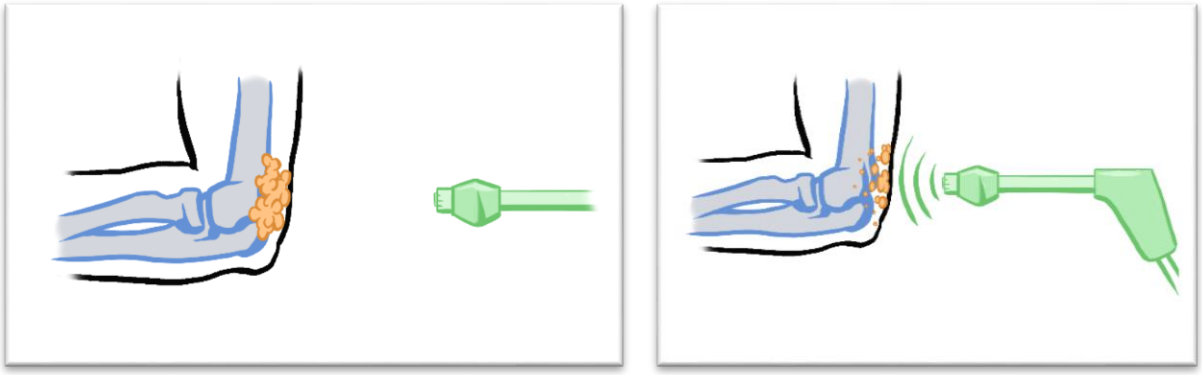

Figure 9.5 An illustration of shockwave therapy being used to erode HO formations at the elbow.

To our knowledge there are currently no guideline recommendations on the use of ESWT for HO following acquired brain injury. Overall, there is limited evidence as to the potential effectiveness of ESWT, randomized controlled trials are needed.

9.5.3 Surgical Excision

Surgical excision of the heterotopic bone is most commonly performed when HO has led to marked functional impairment or skin ulceration due to deformity (Brady et al., 2018; Moreta & de los Mozos, 2014; Watanabe & Sant, 2001a). A recent systematic review found that up to 55% of individuals with neurogenic HO required surgical intervention (Almangour et al., 2016). Previously, surgical intervention was not considered until 12 to 18 months after HO initiation (Garland, 1991; Sazbon et al., 1981). However, more recent studies have shown earlier surgical intervention decreases rates of recurrence, osteopenia, and ankylosis (Almangour et al., 2016; Genet et al., 2012; Moreta & de los Mozos, 2014).

Multiple studies have found positive results on range of motion, functioning, and decrease in recurrence after the surgical excision of HO (Fuller et al., 2013; Genet et al., 2012; Pansard et al., 2013). Overall, the literature provides two unique observed correlations: 1) lower rates of neurological damage were linked to improved outcomes (de Palma et al., 2002), and 2) longer wait times before excision were show to correlate with poorer outcomes (Lazarus et al., 1999). **The Clinical Practice Guidelines for the Rehabilitation of Adults with Moderate to Severe TBI recommend the use of surgical excision for the management of late stage HO (INESSS-ONF, 2015).**

Unfortunately, there is no true consensus with respect to the rates of recurrent HO following surgery. As study protocols vary, so do follow-up and classification methods of HO, making the correlations between surgery and recurrence that much more challenging to understand.

9.6 Prevention of Heterotopic Ossification

Although certain risk factors have been identified for HO formation, preventative treatment is challenging as development of HO is hard to predict. Preventative interventions for HO include passive range of motion exercises, nonsteroidal anti-inflammatory medication, and etidronate disodium (Watanabe & Sant, 2001a), these are described further in Table 9.3.

Table 9.3 Prophylactic interventions for heterotopic ossification.

Intervention	Description	References
Passive range of motion exercises	Passive range of motion exercises can be applied by either a therapist or by a machine. In total knee replacement, passive range of motion exercises maintained range of motion. Further there is little evidence that range of motion exercises worsen HO.	(Linan et al., 2001; Nadler et al., 1993; Salter, 1993)
Etidronate disodium (EHDP)	EHDP works by preventing the aggregation, growth, and mineralization of calcium hydroxyapatite crystals, which are essential for bone formation. The use of EHDP is considered controversial and has been associated with osteomalacia. A single prospective study (1983) found reduced rates of HO formation in those with an ABI compared to controls.	(Spielman et al., 1983; Watanabe & Sant, 2001a)

The Clinical Practice Guideline for the Rehabilitation of Adults with Moderate to Severe TBI do not make any recommendations on the use of prophylactic interventions for the formation of HO.

9.7 Heterotopic Ossification Case Study

Patient Snapshot:

Mrs. Y is a 36-year-old female that was involved in a MVC. She sustained a severe ABI and non-displaced hip fracture with extensive bruising. Her recovery required a 4-day stay in the ICU and mechanical ventilation. Ten weeks following the MVC, she now has right-sided spasticity and her right hip has pain with decreased range of motion.

Q1. What risk factors of heterotopic ossification does Mrs. Y have?
Skeletal trauma, spasticity, mechanical ventilation, prolonged immobilization, hematoma

Q2. How is heterotopic ossification diagnosed?
Signs and symptoms include: restricted range of motion, swelling, warm, painful joints. A diagnosis can be made by a positive CT scan, bone scan, or ultrasound. X-ray imaging may not show findings until 4-6 weeks post injury. A bone scan is considered the gold standard.

Case Continued:

An X-ray of the pelvis revealed bony changes, and heterotopic ossification was confirmed by CT: multiple bone islands up to 1.2 cm in length, and bony spurs at the pelvis and femur separated by a 0.8 cm space.

Q3. What stage of heterotopic ossification is seen based on the original Brooker classification?
Stage III

Q4. What grade of heterotopic ossification is seen based on the Della Valle modified Brooker classification?
Grade C

Q5. What are her treatment options?
-Bisphosphonates (etidronate), NSAIDs (indomethacin)
-Passive range of motion physiotherapy and forceful manipulation under anesthesia
-Surgical excision
-Extracorporeal Shockwave Therapy and radiotherapy (limited evidence)

These treatment modalities have been used in combination to improve outcomes and prevent recurrence.

Q6. Which preventative treatments may have helped given Mrs. Y suffers from a severe ABI?
Patients with moderate to severe ABI should be screened for heterotopic ossification. Prophylactic bisphosphonate (etidronate), NSAIDs and passive range of motion physiotherapy have shown benefit although the *Clinical Practice Guideline for the Rehabilitation of Adults with Moderate to Severe TBI* do not make any recommendations for prophylactic interventions.

9.8 Introduction to Venous Thromboembolism

Venous ThromboEmbolism (VTE) includes both Deep Vein Thrombosis (DVT) (Figure 9.6) and Pulmonary Embolisms (PE) (Figure 9.7). DVT occurs when a clot forms within a deep vein, almost always in the legs, while PE refers to a clot which has dislodged and travelled to the lungs (Office of the Surgeon et al., 2008). VTE still remains a common issue following moderate to severe ABI. Scientific evidence for VTE interventions is comprehensively summarized in the ERABI chapter. Please **Click here to see the online ERABI module on VTE**

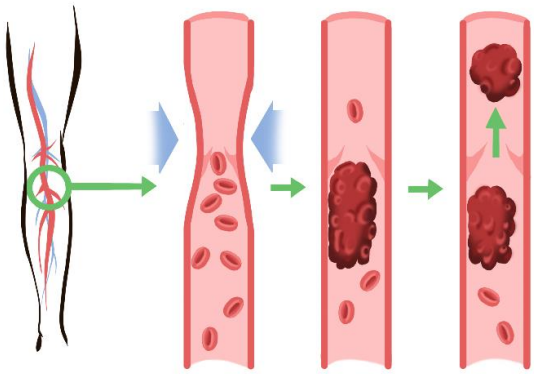

Figure 9.6 An illustration of a clot forming in the lower limb of an individual who has decreased blood flow.

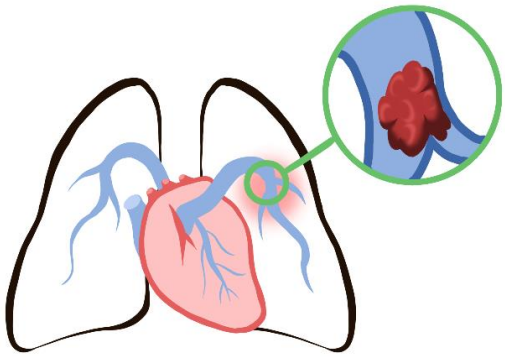

Figure 9.7 An illustration of a clot which has broken off in a vein and resulted in a pulmonary embolus.

9.9 Clinical Presentation and Features of VTE

9.9.1 Incidence of VTE Following ABI and Risk Factors

The reported incidence of DVT among patients with TBI ranges from 11% to 54% (Carlile et al., 2010; Cifu et al., 1996; Denson et al., 2007; Geerts et al., 1994). In the absence of prophylaxis, the estimated risk of developing DVT or PE is 20% (Haddad & Arabi, 2012). Decisions on how to treat individuals with VTE or at high risk of VTE is often assessed individually. Therefore, the **Clinical Practice Guideline for the Rehabilitation of Moderate to Severe TBI makes the following treatment recommendations (INESSS-ONF, 2015);**

- **Venous thromboprophylaxis should be initiated as soon as medically appropriate following TBI**
- **Low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin (UFH) for venous thromboprophylaxis after TBI.**
- **When pharmacological venous thromboprophylaxis is contraindicated or delayed after TBI, physical methods (i.e., intermittent pneumatic compression stockings) should be utilized.**

Virchow's triad (Figure 9.8) identifies the three primary risk factors for VTE, which are venostasis, vessel wall injury, and hypercoagulability (Watanabe & Sant, 2001a). Currently, there appears to be no known association between VTE incidence and initial Glasgow Coma Scale scores, Injury Severity Scale scores, or Abbreviated Injury Scale scores (Denson et al., 2007). However, VTE appears to have a positive relationship with length of stay in the intensive care unit as well as the number of days spent on a ventilator (Denson et al., 2007). Those at highest risk post injury are those who remain on a ventilator longer than 3 days (Olufajo et al., 2016; Raslan et al., 2010). At 1-year post injury, risk of VTE is greatest for those discharged to extended care facilities compared to home, and for individuals who undergo an operation (Olufajo et al., 2016). Two studies have suggested that individuals who sustain a TBI but no vessel injury may still be at an increased risk of VTE as a result of a trauma-induced hypercoagulable state (Geerts et al., 1994; Geerts et al., 1996). The understood recurrence rate of VTE provoked by major trauma or surgery is 1% at one year after stopping coagulation, and 3% at five years after stopping coagulation (Tran et al., 2019a).

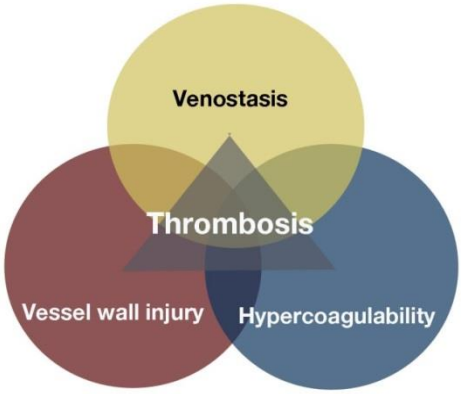

Figure 9.8 Virchow's triad, showing the primary factors in the formation of thrombi.

9.9.2 Pathophysiology of VTE

The formation of VTE thrombi requires one or more of the factors in Virchow's triad. Hypercoagulability, which is an increase in the propensity for blood coagulation, can contribute to the formation of thrombi and is influenced by deficiencies in AntiThrombin (AT), Protein C (PC), Protein S (PS), and Plasminogen (Pg) (Tapson, 2008). As previously mentioned, individuals with an ABI may enter a temporary hypercoagulable state (Geerts et al., 1994; Geerts et al., 1996) where these factors may be altered. Individuals are often immobile for long periods of time following an ABI, this contributes to venous stasis, the second risk factor in developing VTE. The last factor, vessel wall damage or endothelial damage, contributes to the formation of thrombi in multiple ways. First, endothelial damage introduces exothelial factors (such as collagen) to the blood which can encourage clotting (Charlebois, 2005; Tapson, 2008). The overproduction of red blood cells can also lead to hyperviscosity, ultimately resulting in a stasis of blood in the veins, particularly when in combination with prolonged immobility (Charlebois, 2005).

For DVT specifically, when venous valves experience a reduction in oxygenation the endothelium becomes hypoxemic. This causes the endothelium to release adhesion molecules ultimately initiating a coagulation cascade resulting in the production of fibrin (Kearon, 2003; Line, 2001; Morris, 2011). Fibrin and red blood cells make up the main components of thrombi (Kearon, 2003; Line, 2001; Morris, 2011).

9.9.3 Clinical Presentation of VTE

The majority of deep venous thrombi form below the iliac level, with approximately 28% isolated to calf veins (De Maeseneer et al., 2016). Although the signs and symptoms of PE may be sudden and severe, silent PE has become the subject of multiple recent publications (Garcia-Fuster et al., 2014). The incidence of silent PE in those with DVT has been found to be 11-59% (Garcia-Fuster et al., 2014). Although both DVT and PE may have significant observable signs and symptoms, silent cases occur in both. If DVT or PE are suspected, additional clinical tests should be immediately initiated. Multiple diagnostic algorithms are

discussed in Section 9.11 Criteria for Diagnosis to support the accurate diagnosis of DVT and PE. Clinical symptoms of both DVT and PE are presented in Table 9.4.

Table 9.4 Clinical Signs and Symptoms of DVT and PE (taken from www.thrombosiscanada.ca)

Type of Obstruction	Signs and Symptoms
Deep venous thrombosis	- Pain, tenderness - Swelling of the affected segment - Redness, discoloration of affected segment - Visibility of skin veins
Pulmonary embolism	- Sudden shortness of breath - Increased heart rate - Chest pain - Pain with breathing - Dizziness

9.10 Clinical Assessments for VTE

Q4. What is currently the gold-standard assessment to confirm a diagnosis of DVT? PE?

1. Magnetic resonance venography or ultrasound.
   Computed tomography pulmonary angiogram.

9.10.1 D-dimer Assay

A D-dimer assay is a blood test which assesses the concentration of D-dimer in the blood stream. D-dimer is a component of a protein which breaks down clots in the body. High concentrations of D-dimer can be an indication of a clot, however further tests are usually conducted. Overall, this test is **not used to exclusively diagnose VTE** because it can be confounded by other coexisting processes; therefore, it simply provides information for a broader context.

9.10.2 Magnetic Resonance Venography and Contrast Venography

A venogram assesses the blood flow within a vein or system of veins. Contrast venography (x-ray) was once considered the gold standard for the diagnosis of DVT with a reported sensitivity ranging from 70-100%, and specificity from 60-88% (Albert et al., 2008). However, as x-ray venograms are invasive they are typically only used now when an ultrasound yields negative results, despite positive patient symptoms. During an x-ray venogram, contrast dye is injected into the foot and is read by a trained radiologist. Magnetic Resonance (MR) venograms use radio frequency pulses to align hydrogen atoms with tissues and measure the signals of the atoms as they return to their natural state. As blood clots emit different signals from flowing blood, MR venograms can be used to detect thrombi.

The specific advantages of MR venograms are that they give much more accurate images of veins in the pelvis, abdomen, and chest compared to ultrasounds, they do not require compression, and they can be performed through casts (Zhang et al., 2019). MR venograms have been found to have a sensitivity of 94.7% and a specificity of 100% for detecting DVT (Lindquist et al., 2010). Although previously no statistical differences in the diagnostic performance of MR venograms and ultrasounds have been reported (Lindquist et al., 2010), one recent meta-analysis has reported greater diagnostic accuracy in venography compared to ultrasounds (Zhang et al., 2019).

9.10.3 Computed Tomography Pulmonary Angiogram

The preferred choice of imaging for PE is a Computed Tomography Pulmonary Angiogram (CTPA) (Fedullo & Tapson, 2003). As modern CT machines are able to deliver images in a shorter amount of time, combined with the limited invasiveness of this assessment, CTPA has become the clinical gold standard for diagnosing PE (Apfaltrer et al., 2011). To conduct the assessment, patients receive an intravenous injection of a contrast agent which circulates through the pulmonary vessels and appears bright white (Figure 9.9).

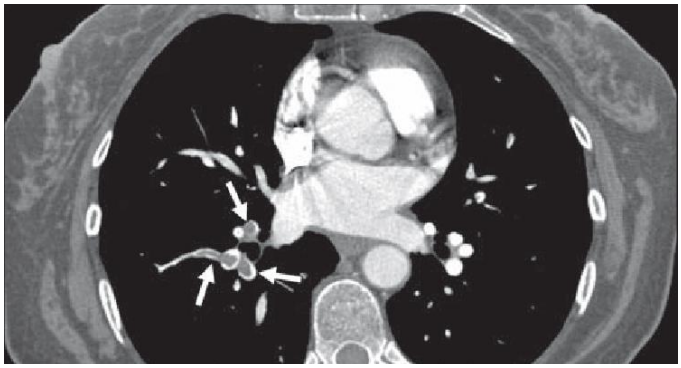

Figure 9.9 A pulmonary angiogram with arrows pointing to a pulmonary embolism (Stein et al., 2010).

It should be noted that CTPA is not recommended for women who are pregnant as high concentrations of iodine, as well as radiation exposure, can negatively impact the fetal thyroid gland (Scarsbrook & Gleeson, 2007).

9.10.4 Ultrasonography

The sensitivity and specificity of ultrasonography ranges 95-99% for the detection of DVT (Lindquist et al., 2010). Ultrasounds are typically the first assessment performed when DVT is suspected. During the procedure the sonographer attempts to collapse and compress the veins within the legs, if a vein cannot be compressed due to the presence of a clot, then a diagnosis of DVT is confirmed (Pellecchia et al., 2009). Compressions are typically conducted along the popliteal vein, the common femoral vein, and the superficial femoral veins (Pellecchia et al., 2009).

However, it should be noted that a recent meta-analysis of 41 studies found that the missed diagnosis rate of lower-limb DVT when individuals were asymptomatic was up to 50% (Zhang et al., 2019). The authors strongly caution that a negative ultrasound does not preclude the presence of DVT and individuals should be continually monitored (Zhang et al., 2019).

9.10.5 Pulmonary Ventilation (V) and Perfusion (Q) Scan

The preferred diagnostic investigation in pregnant women or patients with renal impairment is VQ scanning, as it does not require radiocontrast (Tran et al., 2019b). Palmowski et al. (2014) reported the sensitivity and specificity of VQ scanning as 95.8% and 82.6%, respectively, with false negative rates of 4.2% and false positive rates of 17.3%. Hence, if normal, a VQ scan effectively excludes a PE (Sostman et al., 2008). Identified perfusion defects are non-specific and only represent true PE in about one-third of patients. The remaining proportion of patients may have non-diagnostic scans, which require further testing with CTPA to exclude PE (Anderson et al., 2007). The probability that a perfusion defect represents a PE increases with the size, shape, and number of defects as well as the presence of a normal ventilation scan.

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED Investigators) study demonstrated that a low-probability or normal ventilation-perfusion scan with a low clinical suspicion of PE essentially excludes the diagnosis of PE (negative predictive values of 96% and 98% respectively) (Gill & Nahum, 2000; Investigators, 1990). When clinical suspicion is high and the scan indicates a high probability of PE, the positive predictive value is 96% (Gill & Nahum, 2000; Investigators, 1990), and these patients should be treated. The majority of ventilation perfusion scans have non-diagnostic results, requiring further testing (Investigators, 1990). For this reason, in addition to limited availability of VQ scans, CTPA is the preferred investigation for PE imaging.

9.11 Criteria for Diagnosis of VTE

Q5. What free clinical resources currently exist to facilitate the diagnosis and management of VTE?

1. The Evidence-Based Review of Acquired Brain Injury (ERABI) (https://erabi.ca/)
2. The Clinical Practice Guideline for the Rehabilitation of Adults with Moderate to Severe TBI (http://braininjuryguidelines.org/)
3. The New Guidelines for the Diagnosis and Management of Venous Thromboembolism from the Thrombosis and Haemostasis Society of Australia and New Zealand (https://www.thanz.org.au/resources/thanz-guidelines)
4. Thrombosis Canada (https://thrombosiscanada.ca/)

Recently published guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand (Tran et al., 2019a) make the following recommendations regarding the diagnosis of VTE and PE. The complete publication can be accessed here.

Recommendations from the 2019 Guidelines for the Diagnosis and Management of Venous Thromboembolism from the Thrombosis and Haemostatis Society of Australia and New Zealand (Tran et al., 2019a).

- "A non-high pre-test probability combined with a negative D-dimer result safely excludes VTE without imaging." (GRADE: Strong; Evidence: High)
- "A single negative complete ultrasound is sufficient to exclude DVT." (GRADE: Strong; Evidence: High)
- "A negative technically adequate CTPA excludes PE and anticoagulation can be safely withheld." (GRADE: Strong; Evidence: High)

Regarding the diagnosis of PE**,** Anderson et al. (2007) has published two diagnostic algorithms; one utilizing CTPA, and the other using ventilation-perfusion scanning. It recommends that in the presence of a negative CTPA (despite positive symptoms), a leg vein ultrasonography and D-dimer assay should be conducted to provide more insight as to the cause of symptoms. It should be noted that these algorithms are designed to facilitate the diagnosis of PE in the average patient and have not been designed specifically to diagnose PE in those with ABI.

A separate clinical algorithm has been published by Wilbur et al. (2012) for the diagnosis of DVT. After DVT is suspected due to the presence of observable signs and symptoms, if the risk is high a compression ultrasonography is recommended, should the results be negative a D-dimer assay is recommended to confirm the absence of DVT (Wilbur & Shian, 2012). Similar to the above algorithms, this algorithm was not designed to be specifically applied to the ABI population and should be combined with clinical judgment in its use and execution.

9.12 Interventions for the Prevention and Management of VTE

The following interventions and studies discussed are taken from the ABI literature. Although other interventions may be suitable for the prevention and management of VTE, only those which have been examined in the ABI population are presented below. Several interventions have been examined for the prevention of DVT after an ABI, including mechanical therapy, pharmaceuticals, or a combination of both. In a systematic review, Hachem et al. (2018) found rates of VTE in patients with severe TBI not receiving anticoagulation prophylaxis were near 30%, compared to 5-10% of patients with prophylaxis. However, there is no agreement on the administration of these medications in terms of timing, dose, and/or which anticoagulation medication.

Thrombosis Canada offers live free clinical algorithms to support the management of DVT and PE, practitioners are able to input specific patient information receive an evidence-based recommendation. These free clinical tools can be accessed here at https://thrombosiscanada.ca/tools/ .

9.12.1 Compression Devices

Compression devices such as thromboembolism deterrent stockings, and intermittent pneumatic compression devices including arteriovenous foot pumps and sequential compression devices (SCDs) (Figure 9.10) are used to prevent the development of DVT post-ABI. These devices operate primarily through two distinct mechanisms of action. The first is mechanical, in which the device increases the velocity of venous return to decrease venous stasis, thus reducing the opportunity for clot formation. The second, and perhaps more important mechanism, involves the systemic activation of the fibrinolytic system which, during compression, leads to the breakdown of fibrin clots associated with thromboembolism (Macatangay et al., 2008).

Figure 9.10 An example of an intermittent compression device used for the prevention of DVT.

Overall, there is limited evidence in the ABI literature to support that compression devices are an effective prophylactic, particularly compared to low-molecular-weight heparin (Gersin et al., 1994; Kurtoglu et al., 2004; Minshall et al., 2011; Praeger et al., 2012). Multiple studies have found no significant differences between those who were treated with compression devices compared to those treated with pharmacological prophylaxis (Gersin et al., 1994; Kurtoglu et al., 2004). However, leg compressions were not shown to negatively impact venous pressure, intracranial pressure, or cerebral perfusion pressure (Davidson et al., 1993).

9.12.2 Pharmacological Prophylaxis

A recent systematic review has found that anticoagulant prophylaxis does significantly reduce the incidence of VTE in those with an ABI from 30% to 5-10% (Hachem et al., 2018). Multiple pharmacological agents have been investigated as a prophylactic treatment for VTE. Warfarin (Coumadin), a well-established anticoagulant with a predictable duration of action, is increasingly avoided as a prophylactic alternative for DVT due to its elevated bleeding side effects (Watanabe & Sant, 2001a). Albrecht et al. (2014) report that warfarin use is associated with lower rates of DVT and PE, but comes at the cost of the risk of increased hemorrhagic bleeding. However, some experts felt the use of warfarin was advisable, especially for high risk patients due to its benefit in treating undetected thrombosis; the therapeutic dose range for prophylaxis and treatment of thromboembolism are the same (Hirsh et al., 1992; Hyers et al., 1992; Landefeld & Goldman, 1989). Warfarin is typically dispensed at 5-10 mg/day, with treatment lasting at least three months (Ramzi & Leeper, 2004). A large retrospective study of 932 individuals with anticoagulant medication found no association between low-molecular-weight heparin, unfractionated heparin, and Coumadin and increased intracranial or systemic hemorrhaging (Carlile et al., 2010).

The Clinical Practice Guideline for the Rehabilitation of Adults with Moderate to Severe TBI recommend initiating thromboprophylaxis as soon as is medically appropriate (INESSS-ONF, 2015).

Ultimately, there is only limited to moderate evidence to suggest that pharmacological prophylaxis is effective for reducing rates of VTE in ABI populations (Daley et al., 2015; Phelan et al., 2012; Seifi et al., 2018). Similarly, no significant differences in risk have been found for early compared to late prophylactic initiation (Byrne et al., 2016; Hachem et al., 2018; Meyer et al., 2016). Although those who receive early compared to late prophylaxis may not differ significantly in the number of thrombotic events, those who received early intervention had significantly greater cumulative neuro improvement (Kim et al., 2014).

Although the literature presents diverse results, if individuals are haemodynamically stable and have a non-iliofemoral DVT or submassive PE (systolic BP>90mmHg) anticoagulation therapy is indicated according to the Australian and New Zealand Guidelines for the Diagnosis and Management of Venous Thromboembolism (Tran et al., 2019a). Regarding treatment of VTE, clinical judgement should be used to determine the preferred agent. In stable patients with sub-massive PE, LMWH is often the first choice: Dalteparin 200 units/Kg subcutaneously once daily is used (Jaff et al., 2011).

9.12.3 Surgical Management of VTE

In the event of a massive PE (systolic BP<90mmHg for 15 minutes or signs of shock) thrombolysis, surgical embolectomy, or a catheter-based intervention should be considered (Tran et al., 2019a). In these instances, antithrombotic agents may be directly injected into the clot via a catheter or the clot may be surgically removed. These pharmaco-mechanical thrombi interventions are also applicable to DVT (Tran et al., 2019a). Unfortunately, to our knowledge no studies examining the surgical evacuation of VTE in those with an ABI.

9.13 VTE Case Study

Patient Snapshot:

Mr. K is a 68 year-old male with a history of a TBI 11 months ago, which resulted in hemiplegia of his right side. He remains at an extended care facility and spends most of his day in bed, only transferring to a chair for meals. He complains of a two-day history of unilateral leg swelling, pain and redness. Pitting edema, prominent superficial veins and calf swelling of 4 cm is noted in his right leg. It is known that his daughter has had a pulmonary embolism in the past.

Q1. What risk factors of VTE does Mrs. K have?

TBI, paralysis of lower extremity, stasis, extended care facility, family history, male

Q2. According to the Simplified Wells score for DVT, is a DVT likely or unlikely?

Likely. He has 2 or more points when you consider his immobility and paralysis, leg and calf swelling, pitting edema, collateral superficial veins.

Q3. What diagnostic test should be ordered based on your clinical suspicion?

Magnetic resonance venography is gold standard, but an ultrasound is less invasive. A D-dimer is not appropriate in this case because of its low positive predictive value and is best used in cases of low clinical suspicion to help rule out a DVT.

The ultrasound of deep veins revealed occlusion of the popliteal and femoral vein.

Case Continued:

Mr. K developed an acute change to his breathing while waiting for the ultrasound report. He complains of dyspnea and pleuritic chest pain. You notice his heart rate is 115 bpm.

Q3. You suspect Mr. K developed a pulmonary embolism. What is the Wells score for PE?

Wells score for PE indicates a PE is likely and imaging is warranted.

Q4. What type of imaging should you order?
CTPA or VQ scan

CT pulmonary angiography confirmed a pulmonary embolism. What treatment options should be considered?

Proximal DVT and PE should be treated with 3 to 6 months of anticoagulation. DOACs and warfarin are equally effective in this case; however, DOACs are preferred because of their convenient mode of administration. Anticoagulation beyond the initial 3 to 6 months should be considered because his immobility is a persistent risk factor.

Q5. How does TBI affect treatment choice?

Absolute contraindications for anticoagulation include acute intracranial hemorrhage, active bleeding and major trauma. If the patient's TBI involved these contraindications within the last 30 days then they should not receive anticoagulation, and surgical/mechanical clot retrieval should be considered.

Q6. Is there any concern about recurrence?
Yes. Mr. K's risk factors persist and therefore he is at risk of recurrence and a maintenance dose of anticoagulation would be recommended considering no contraindications are present.

Q7. What agent should be used for thromboprophylaxis?

LMWH is preferred for hospitalized patients without bleeding risk. Elastic compression stockings and intermittent pneumatic compression is recommended for patients with contraindications to anticoagulants. Hematology and interventional radiology should be consulted for high risk patients with anticoagulant contraindications to determine suitability of an IVC filter.

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