Endothermal Heat Induced Thrombosis

Endotherme hitzeinduzierte Thrombose

Authors
Mikel Sadek[1], Lowell S. Kabnick[2]

Affiliations
1 NYU Langone Health, New York, USA
2 United Vein Centers, Tampa, USA

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Lowell S. Kabnick, MD, RPhS, FACS, FAVLS, FAVF
United Vein Centers, 3657 Madaca Lane, Tampa, FL 33618, USA
lsk@lowellkabnickmd.com

ZUSAMMENFASSUNG

Die endotherme hitzeinduzierte Thrombose (EHIT) ist eine postoperative Erscheinung nach der endothermen oberflächlichen Venenablation, die sich auf die Verschleppung eines Thrombus in das angrenzende tiefe Venenlumen bezieht. Sie wird meist beim Duplex-Ultraschall zur Kontrolle der Vene nach dem Verfahren erkannt. Die EHIT wird als eine einzigartige postoperative Erscheinung anerkannt, die sich im klinischen Verhalten von einer tiefen Venenthrombose unterscheidet. Definition, Klassifikationssysteme, Pathophysiologie, Risikofaktoren, Behandlung und Prävention werden in diesem Zusammenhang diskutiert. Das Verständnis der EHIT ist inzwischen weit fortgeschritten, aber es sind noch weitere Daten erforderlich, um ihre Auswirkungen auf die Lebensqualität und die Kosteneffizienz der Überwachung zu verstehen.

ABSTRACT

Endothermal heat induced thrombosis (EHIT) is a post-procedural entity following endothermal superficial venous ablation that refers to the propagation of thrombus into the adjacent deep vein lumen. It is identified most commonly during the post-procedural surveillance venous duplex ultrasound. EHIT is recognized as a unique post-procedural entity, distinct in clinical behavior from a deep vein thrombosis. The definition, classification systems, pathophysiology, risk factors, treatment, and prevention are all discussed. The understanding of EHIT has advanced considerably, but additional data are required to understand its impact on quality of life and the cost-effectiveness of surveillance.

Introduction

Chronic venous insufficiency remains a significant problem, and endothermal ablation has revolutionized the treatment of chronic venous insufficiency. The two most well-established modalities of treatment have been radiofrequency ablation (RFA) and endovenous laser ablation (EVLA). Coupled with the use of tumescent anesthesia, endothermal ablation has demonstrated a track record of safety and efficacy. With time, the durability of the procedures has also been validated, and RFA/EVLA are widely accepted as the standard of care for the treatment of symptomatic superficial venous reflux. Moreover, the expansion of access to care has also advanced due to the ability to perform the procedure in an outpatient setting. The supporting data are reflected in numerous guidelines, including the AVF / SVS guidelines for the treatment of chronic venous insufficiency, whereby endothermal ablation, as compared to surgical saphenectomy, is the preferred treatment [1].

One potential consequence of endothermal ablation is the development of endothermal heat induced thrombosis (EHIT). Initially, there was uncertainty regarding this post-procedural entity, and it was unclear if it should be described and treated as a deep vein thrombosis (DVT), addressed as a benign entity, or treated as something else entirely [2]. There was also lack of consistency in reporting, making it very challenging to glean conclusions from the reported data. In 2006, Kabnick introduced and formalized the concept of EHIT to account for the differing clinical behavior between EHIT and DVT [3].

The definition and categorization of EHIT ensued, and multiple reports have since made reference to this entity. Over time, the standardization in reporting has allowed for improved evaluation and collation of the data. More information and high-quality evidence are required to better delineate the pathophysiology, risk factors, treatment and prevention, but the data culminated recently in the development of the American Venous Forum – Society for Vascular Surgery (AVF-SVS) EHIT guidelines [4, 5].

Definition

EHIT relates to the post-procedure phenomenon following an endothermal ablation, whereby there develops propagation of thrombus from the great saphenous vein (GSV) or the small saphenous vein (SSV) into the adjacent common femoral or popliteal vein, respectively. This typically occurs within 72 hours following treatment, but the definition of EHIT may still be met if the thrombus extension is identified within 4 weeks of treatment [6, 7]. In addition, the definition of EHIT may be generalized to the other junctional tributaries, such as the anterior accessory saphenous vein.

The definition of EHIT is distinct from a direct thermal injury to the deep vein, which may be caused by error in visualizing the tip of the catheter. The definition is also distinct from a deep vein thrombosis occurring elsewhere in the venous circulation (e. g. a non-contiguous gastrocnemius or soleal vein DVT) or in the contralateral limb. Lastly, EHIT refers specifically to the thrombus extension that may occur following endothermal ablation; however, EHIT does not include the entity of thrombus extension following other treatment modalities, such as may also occur with the non-thermal, non-tumescent techniques [8].

Classification Systems

Integral to the definition of EHIT is the classification of EHIT. Two prominent classification schemes have populated the literature, the Kabnick classification, and the Lawrence classification. There are differences, but also significant similarities, between the two systems, and these have allowed for consistency in reporting, prognosis and treatment. Moreover, the similarities have allowed for the development of the unified AVF-EHIT classification, and the latter represents the keystone of the AVF-SVS EHIT guidelines [4, 5].

Although EHIT may be diagnosed using various modalities, including axial imaging (e. g. computed tomography venography and magnetic resonance venography) and direct venography, the classification scheme is based on venous duplex utrasound. This is due to the accuracy of venous ultrasound in the peripheral veins, and the ease of use in performing screening ultrasounds in the outpatient setting. The classification is based on the degree of thrombus propagation into the respective deep vein lumen (i. e. the common femoral vein or popliteal vein). This development was crucial in order to maximize the clinical relevance of the classification scheme so that it may correlate with prognosis, and allow for a graded level of management depending on the extent of the pathology, and enable consistent reporting for quality improvement and research purposes. The Kabnick, Lawrence and AVF-EHIT classifications are delineated in the following tables (▶ **Table 1–3**) [4, 5, 9].

▶ **Table 1** Kabnick Classification [3].

class I	thrombus extension up to the deep venous junction.
class II	thrombus propagation into the deep vein, < 50 %.
class III	thrombus propagation into the deep vein, > 50 %.
class IV	thrombus propagation resulting in occlusive deep vein thrombosis.

▶ **Table 2** Lawrence Classification [9].

class I	thrombus distal to the superficial epigastric vein.
class II	thrombus flush with the superficial epigastric vein.
class III	thrombus flush with the saphenofemoral jucntion.
class IV	thrombus propagation into the common femoral vein and adherent to the wall of the common femoral vein.
class V	thrombus propagation into the common femoral vein consistent with a deep vein thrombosis.

▶ **Table 3** AVF-EHIT Classification [4, 5].

class I	thrombus without propagation into the deep vein. a) peripheral to the superficial epigastric vein. b) central to the superficial epigastric vein and up to the deep vein junction.
class II	thrombus propagation into the deep vein, < 50 % of the deep vein lumen.
class III	thrombus propagation into the deep vein, > 50 % of the deep vein lumen.
class IV	thrombus propagation resulting in occlusive deep vein thrombosis and contiguous with the treated vein.

Pathophysiology

Once again, EHIT is related specifically to the endothermal technologies, and that is the focus of this manuscript. As alluded to previously, the same concept may apply to other modalities of superficial venous ablation, such as the non-thermal, non-tumescent techniques, but it is unclear if the pathophysiology is similar or different. Very interestingly, most EHITs will self-resolve, and this is observed in those cohorts where venous duplex ultrasound is not performed routinely, or performed more than 2 weeks post-procedure, rendering the pathophysiology at baseline of EHIT very different from that of DVT [10].

In the animal model, EHIT has demonstrated both different ultrasound and histologic characteristics as compared to DVT [7]. The findings suggest that inflammation is driving the pathogensis of EHIT. This has been demonstrated by elevated C-reactive protein

and D-dimer levels post-ablation, with sustained inflammatory marker increases starting at 24 hours and lasting up to 30 days post-procedure [6]. The histology for EHIT is characterized by a hypercellular response with more fibroblasts and edema. On ultrasound, EHIT appears more echogenic as compared to DVT, and the ultrasound findings in animals have been corroborated clinically in humans [11].

Risk Factors

Identifying clear risk factors for EHIT has represented a significant challenge. There is significant heterogeneity in the data, and the low incidence of EHIT makes it very challenging to identify consistent factors across studies. Many of the studies have also been retrospective in nature, and the various biases have come into play accordingly. Having delineated the limitations, some potential risk factors have been identified, and many correlate to risk factors for venous thromboembolism.

With regards to having a history of venous thromboembolic disease (i. e. DVT or pulmonary embolus), or a history of superficial vein thrombosis (SVT), the data have been suggestive but inconsistent. Some studies have found associations between DVT and EHIT, or SVT and EHIT, but others have not shown any correlations [12–14]. The Caprini score has also been used to try to stratify risk, with a possible cutoff score of greater than 6 as a marker for a risk for EHIT, but again the data have been inconsistent [15, 16].

Age and sex have also been shown as possible risk factors for EHIT, with male sex, female sex, and old age (i. e. age over 65 years old) all having been demonstrated as significant risk factors; however, for every study that has a shown a difference, another study has shown no significant difference [14, 16, 17].

Anatomically, larger vein diameter has come up as a recurring theme, with great saphenous vein diameters of larger than 8 mm or 11 mm and small saphenous vein diameters of larger than 6 mm as cutoffs for a potentially increased risk for EHIT [13, 15, 18, 19]. This may matter more for the central GSV (i. e. large vein near the junction), but again the data are inconsistent [19].

EHIT Treatment

The recommended treatment varies from observation to treatment with therapeutic anticoagulation. In general, the treatment modality is guided by the clinical classification, but it is also dictated by other factors such as the clinical context and clinician judgement. The recommendations are also the same for EHIT associated with the GSV or with the SSV [13, 20]. The goals of treatment are to prevent a clinically significant deep vein thrombosis or pulmonary embolus, both of which have been reported rarely in the literature as sequelae of endothermal ablation.

Recommendations for treatment have been based previously on the Kabnick and Lawrence Classifications. The following represent the most recent recommendations put forth by the AVF-SVS guidelines and are based on the unified AVF-EHIT classification system [4, 5]. As the unified phrasing suggests, these are designed to be comprehensive and to cohesively and consistently incorporate previous recommendations.

EHIT I Treatment

There is no indication for additional treatment or surveillance for this entity [4, 5]. The data behind this recommendation are based on overwhelming evidence that this is a benign entity. Even though previous authors have suggested treatment, the natural history has shown no evidence, or very limited evidence, of propagation with or without treatment [21, 22]. In one study in particular, EHIT 1 was treated in half of the cases, and regardless of treatment there was no incidence of thrombus propagation into the deep vein [9]. A distinction has been made for EHIT that terminates peripheral or central to the superficial epigastric vein (i. e. Ia vs Ib), but this is largely for research purposes and to allow for comparison to the historical literature.

EHIT II Treatment

The recommendation is that no treatment is suggested for EHIT II, but that weekly ultrasound surveillance should be undertaken until there is documented thrombus resolution to the level of the saphenofemoral or saphenopopliteal junction [4, 5]. Alternatively, if the patient is deemed high-risk in the opinion of the clinician, treatment may be initiated with antiplatelet therapy, prophylactic anticoagulation, or therapeutic anticoagulation again until there is documented thrombus resolution on ultrasound [4, 5].

This remains the most common EHIT that is diagnosed clinically, and it is also the most controversial in terms of treatment. Moreover, use of the new anticoagulation agents (i. e. the direct oral anticoagulants), has changed the ease with which patients can be treated. Many of the prior recommendations were based in the context of treating with full anticoagulation using low molecular weight heparin (LMWH) or Warfarin [23].

In one study, 61 cases of EHIT II were identified out of 4906 GSV treatments, and antiplatelet therapy or observation was employed. There were three cases that developed thrombus propagation, and those cases were transition to full anticoagulation with subsequent full resolution [21]. One study demonstrated that in 19 patients observed with EHIT II, in whom 6 of the 19 were anticoagulated, and the rest were observed, complete thrombus resolution was noted in all patients [18].

EHIT III Treatment

The recommendation is slightly stronger towards therapeutic anticoagulation, again with weekly ultrasound surveillance until there is documented thrombus resolution [4, 5]. There are very limited data to support this recommendation, but the increased burden of thrombus (i. e. > 50 % of the deep vein lumen), coupled with the greater ease of anticoagulation using the novel agents, and the rarity of this entity that prevents a prospective evaluation, are the basis for this recommendation [24].

EHIT IV Treatment

Given that EHIT IV is defined as an occlusive thrombus, but also recognizing that the pathophysiology is different as compared to a de novo DVT, the recommendation is once again to individualize

treatment to the patient based on thrombotic and bleeding risk [4, 5]. For additional guidance, reference may be made to the CHEST guidelines for the treatment of acute DVT, possibly with special attention to the management of the acute provoked DVT [25].

EHIT Prevention

Subsequent to the identification and characterization of EHIT, there have been numerous anecdotal ways to mitigate the incidence of EHIT. One strategy is to remain cognizant of an underlying hypercoagulable state and to consider the administration of prophylactic anticoagulation in the peri-procedural period in certain high-risk cohorts. Some examples of high-risk characteristics include patients with a history of venous thromboembolic disease, patients with a history of superficial thrombophlebitis, or patients with a known genetic hypercoagulable state, and some protocols have been developed accordingly [16].

As additional data have been gathered, specific recommendations have been put forth, particularly with regards to the use of mechanical and chemical prophylaxis. Mechanical prophylaxis in this context refers to the use of compression stockings in the peri-procedural period.

Numerous series have looked at elastic compression in the peri-procedural period with the 20–30 mmHg and 30–40 mmHg strengths being used the most commonly. Ultimately, there was no correlation between the use of stockings and the development or reduction of EHIT [15, 19, 26, 27].

With regards to chemical prophylaxis, peri-procedural unfractionated heparin as well as LMWH have both been evaluated. In summary, no study has demonstrated a decreased risk of EHIT with the use chemical prophylaxis. In one particular study all patients who developed an EHIT had received prophylaxis, suggesting a possible selection bias [28]. Others have attempted treatment based on risk factors but have not shown a difference in the rate of EHIT [29].

As a corollary, it has also been proven safe and effective to perform procedures on patients who are already on full anticoagulation with Warfarin, and therefore anticoagulation is generally continued in patients undergoing endothermal ablation, possibly mitigating the risk of EHIT in this population [30].

There are also procedural techniques that may reduce the risk of EHIT, but data remain forthcoming. One such technique is the aggressive administration of tumescent anesthesia at the saphenofemoral or saphenopopliteal junction to limit heat propagation to the deep vein. Another technique uses the concept of laser crossectomy to ablate at the junction in order to eliminate the development of a reservoir that may allow for thrombus propagation and the development of an EHIT. One trial demonstrated that increasing ablation distance may be beneficial. In particular, initiating ablation 2.5 cm or more from the saphenofemoral or saphenopopliteal junction may mitigate the risk of DVT, and this was shown to be effective with both EVLA and RFA, while still maintaining good long-term outcomes [23].

Conclusions

EHIT is a well-documented entity and is thought to be a relatively benign or manageable condition in the vast majority cases. It is relatively easy to treat using a combination of close observation with venous duplex ultrasound, and antiplatelet or anticoagulant medications as needed. Prevention of EHIT has been a greater challenge, and this is in large part due to its low reported incidence. One strategy is to ablate greater than 2.5 cm for the junction. That being said, additional data are required to better assess the impact of EHIT on quality of life and perhaps the cost-effectiveness for even looking.

Conflict of Interest

The authors declare that they have no conflict of interest.

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