Endovenous Intervention: From the Legs to the Lungs

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Endovenous Intervention: From the Legs to the Lungs

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Abstract

Significant advancement in endovascular technology have enabled the treatment of a variety of venous diseases from the deep vein diseases to diseases in the pulmonary vasculatures. Understanding the principles and the limitations of these endovenous interventions is very important in selecting the appropriate patients for optimal clinical outcomes. In this review, the clinical evidence, guideline recommendations from various societies and the approaches to these endovenous procedures will be discussed.

Keywords: Deep vein thrombosis, Pulmonary embolism, Post-thrombotic syndrome, Chronic thromboembolic pulmonary hypertension, Endovenous, Venous stents

Introduction

Venous diseases encompass a wide array of vascular pathologies that affect the venous vasculature in the circulatory system. While venous thromboembolism (VTE) makes up a majority of the conditions presented to physicians, venous disease can also come in the form of vascular stenosis or vascular compression. Venous diseases can be classified either by (i) chronicity: acute or chronic; or (ii) underlying pathology such as thromboembolic and stenotic; or (iii) locations in the circulatory system such as peripheral, central, or pulmonary. While acute pulmonary embolism (PE) and phlegmasia (severe lower limb deep venous thrombosis which may progress to critical limb ischemia and limb loss) represent the most urgent types of venous disease, other forms of venous diseases such as chronic venous insufficiency (CVI) and chronic thromboembolic pulmonary hypertension (CTEPH) can be associated with significant morbidity and impairment of quality of life [1]. Significant advancement in technology and technique of endovenous intervention have enabled safe and effective treatments of various venous pathologies. In this review, we will discuss the general principles, applications and the clinical evidence of endovenous interventions in the management of various venous diseases.

Principles of endovenous intervention

Endovenous intervention works on the same basic principles of transluminal interventions with a few key differences from transarterial intervention based on the dissimilarities in venous vascular structure and underlying pathologies. Vein is a thin wall vascular structure and a low-pressure system. Its intrinsic vascular support is relatively weaker than arterial system. It is also prone to extrinsic compression especially by adjacent pulsatile arterial structures [2]. Therefore, plain-o-balloon-angioplasty (POBA) tends to yield less durable luminal gain especially in chronically occluded veins, and metallic scaffold is often needed to provide extrinsic support and to maintain luminal patency. Intraluminal venous pressure is usually close to 0 mmHg at the peripheral, and the draining of blood inside the vein depends greatly on the patency of the flow circuit and normal func-
tioning of venous valves which are present in the peripheral veins outside thoracoabdominal cavity [2]. Restoration of patency of the venous conduit with approximation to normal circumference is therefore important to re-establish normal venous circulation. Intravascular imaging such as intravascular ultrasound (IVUS) have been shown to be useful in determining the appropriate stent size and identifying extrinsic compression in endovenous intervention (Fig. 1) [3]. Unlike atherothrombotic occlusion in the arterial system, which is a progression of arterial intimal atherosclerosis, occlusion in the venous system is usually the result of acute thromboembolism or failure of thrombus resolution in chronic stage [2]. While thrombotic occlusions are soft and can be readily recanalized in the acute stage, chronic organized venous thrombus are fibrinous and hard [4], making wires crossing and recanalization more challenging. Moreover, chronic venous occlusion is usually associated with extensive fibrotic changes and scaring of the diseased segment [4], further mandating metallic scaffolding in maintaining lumen patency. Most stents used in endovenous intervention are self-expanding in design. In recent years, a number of dedicated venous stents are available with increased chronic outward force and radial resistive force for scaffolding support and flexibility to accommodate the tortuous venous anatomy [5]. Due to the underlying prothrombotic predisposition, antithrombotic choices post procedure is less well defined than in post-arterial intervention [6].

Endovenous intervention for acute venous thrombosis

VTE is the commonest type of venous disease, with an annual incidence of 55–117 per 100 000 person-years [7]. The cornerstone of VTE treatment is anticoagulation which can retard thrombus propagation and prevent thrombus embolization [8–10]. However, anticoagulation therapy has little thrombolytic properties and will not directly remove thrombus. Conservative measures such as leg elevation and compression stocking can help relieve lower limb symptoms. Patients with severe proximal DVT in the ilio-femoral region can present with venous gangrene or Phlegmasia Cerulea Dolens (Fig. 2). Additional endovenous therapy should be considered to provide more rapid symptom relief, and to prevent the development of acute limb ischemia and post-thrombotic syndrome [8–10] (Table 1).

There are two main endovenous treatment strategies for the treatment of acute DVT: pharmacological using catheter directed thrombolysis (CDT), or mechanical thrombectomy. During CDT, thrombolytic agents is infused directly into the thrombus using either a multi-sideholes infusion catheter or via the EKOS system (Boston Scientific, Natick, MA, USA) which is equipped with ultrasonic probes to facilitate the delivery of thrombolytics (Fig. 3) [11]. Although CDT has been shown to be more effective than anticoagulation alone in preventing post-thrombotic syndrome (PTS) in the CAVENT trial [12], such benefits has not been confirmed in the later randomized ATTRACT and CAVA trials [13,14]. In mechanical thrombectomy, thrombus is removed directly by aspiration using either vacuum suction such as in the Penumbra system (Penumbra, Alameda, California, USA) (Fig. 4), or by the Venturi effect generated from a high velocity saline jet in the Angiojet Rheolytic Thrombectomy system (Boston Scientific, Natick, MA, USA) (Fig. 5). The Angiojet

Fig. 1. IVUS image of left iliac vein. A: IVUS showing LCIV compressed by the RCIA with RCIV shown as reference; B: Distal Left EIV as reference; C: baseline venogram showing underappreciation of LCIV compression on 2D image; D: IVUS pullback; E: venogram post stenting; F: IVUS showing significant enlarged LCIV lumen post stenting; G: IVUS showing well-apposed stent at EIV. LCIV: left common iliac vein, RCIA: right common iliac artery, RCIV: right common iliac vein, EIV: external iliac vein, IVUS: intravascular ultrasound.
system has an additional advantage of being able to infuse thrombolitics using the Power-spray function and thus combining both treatment modalities to achieve a single stage pharmaco-mechanical thrombectomy procedure. This has been shown to be safe and effective as a single-stage procedure in the treatment of phlegmasia [15].

Endovenous intervention for chronic lower limb venous insufficiency

Post-thrombotic syndrome (PTS) is a common long-term complication of acute DVT, affecting an estimated 20–50% of patients with DVT [16,17]. The symptoms and clinical signs of PTS include chronic pain, intractable limb oedema, varicose veins, venous claudication, hyperpigmentation, and venous ulcers [16] (Fig. 2). PTS significantly affects patient’s quality of life and impart a hefty burden on the healthcare system [18,19]. While conservative managements such as leg elevation and compression therapy can be considered in patients with mild PTS, these are generally ineffective in moderate to severe PTS. Invasive interventions, especially endovenous venoplasty can be offered to appropriately selected patients to reduce the symptoms of moderate to severe PTS [8,10] (Table 1).

Unlike acute thrombotic occlusion in acute DVT, venous obstruction in PTS is a result of chronic organized thrombus, fibrotic remodelling of the venous structures and venous hypertension [2]. Therefore, endovenous treatments such as CDT or mechanical thrombectomy are less effective in recanalization and restoring venous flow. Instead, venoplasty with POBA to break-up the organized thrombus, and metallic stents for scaffolding are usually required to restore patency. Moreover, extrinsic compressions at the iliac vein (i.e. May-Thurner Syndrome, Fig. 1) can be demonstrated in significant proportion of patients suffering from severe PTS [20], making metallic scaffolding an important treatment modality in maintaining vascular patency in these patients. In this issue, Ng et al. presented an interesting case of concurrent May-Thurner and Nutcracker syndrome treated by endovenous stenting.

Table 1. Recommendations from various societies on endovascular interventions for venous diseases.

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<td>conditional recommendation based on low certainty of evidence</td>
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<td>Class I; Level of Evidence C for phlegmasia.</td>
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<td>Class IIa, Level of Evidence C</td>
<td>Class IIA, Level of Evidence C</td>
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<td>• Class I, Level of Evidence C for inoperable CTEPH</td>
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<td>• Class IIB Level of Evidence B for operable CTEPH</td>
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Endovenous intervention for central venous stenosis

Central veins refer to both the thoracic central veins (the superior vena cava) and the abdominal central veins (the inferior vena cava). Unlike peripheral veins, the most common aetiology of central venous occlusion is extrinsic compression by malignancy, followed by chronic fibrotic stenosis from prolonged indwelling catheters or devices [21]. Surgical reconstruction or bypass used to be the gold-standard for treatment of central venous stenosis [22,23]. However, surgery is associated with major peri-operative mortality and complications. Endovenous venoplasty with or without stenting has been proposed as an alternative to surgical repair with comparable mid-term and long-term patency rates. Due to the large luminal size of central veins, usually special metallic stents with strong radial force are required to provide adequate

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**Fig. 3. Example of EKOS procedure.** A: placement of EKOS catheter at bilateral pulmonary arteries; B: Component of EKOS catheter; C: integrated control unit; D: position of patient using bilateral brachial veins access.

**Fig. 4. Example of Aspiration Thrombectomy procedure in acute PE using the Penumbra system.** A: Catheter aspiration of Right PA; B: baseline PA angiogram showing bilateral occlusive thrombus; C: catheter aspiration of left PA; D: post PA angiogram showing recanalization of right PA; E: thrombus yielded from the Penumbra procedure; F: post PA angiogram showing recanalization of left PA. PA: pulmonary artery, PE: pulmonary embolism.
scaffolding support [24]. Alternatively, two stents in a double-barrel fashion can be used to match the luminal diameter.

Endovenous intervention for acute pulmonary embolism

Acute pulmonary embolism is the third leading cause of cardiovascular mortality, with an annual incidence of 62–112 per 100 000 person-years [25–27]. While majority of the acute PE are low risk and can be treated conservatively with anti-coagulation therapy alone, some patients especially those with intermediate to high-risk PE (Table 2) and evidence of right ventricular PE dilatation will benefit from additional endovenous intervention to expedite patient recovery and prevent hemodynamic decompensation (Table 1) [8–10,28,29]. The goal of endovenous intervention is to remove or reduce thrombus burden in the pulmonary arteries and relieve the pressure on the right ventricle, speeding up patient recovery and potentially reducing the incidence of subsequent CTEPH. This can be achieved by either infusing low dose thrombolytics via a specialized catheter empowered with ultrasonic emission (the EKOS system, Fig. 3), or by mechanically removing the thrombus using aspiration (the Penumbra system, Fig. 4).

All of these procedures involve endovenous access usually from the femoral veins. During the EKOS procedure, the ultrasonic catheters are placed at the targeted pulmonary arteries for direct infusion of thrombolytics with the assistance of ultrasound which enhance the penetration of thrombolytics into the thrombus and facilitating the fibrinolytic actions. With the ultrasonic assistance, the dosage and the duration of thrombolytics infused is typically less than conventional CDT. The safety and clinical efficacy of EKOS in terms of right ventricular dysfunction resolution have been reported in various registries and randomized controlled trial [30,31]. The penumbra system comprises of aspiration catheters of varied sizes (CAT 6, CAT 8, CAT 12), with bigger size providing greater aspiration, a separator, and a vacuum pump generating a power suction (Fig. 4). Accelerated thrombus clearance and resolution of right ventricular dysfunction were reported in the EXRTACT PE study [32]. While both treatment strategies convey similar safety profile and clinical efficacy, several factors need to be considered in choosing the appropriate treatment for the patient. Firstly, operator expertise and familiarity with the device are important factors in the selection of device. Secondly, the hemodynamic status will determine the urgency of thrombus removal and pulmonary artery recanalization. The clinical improvement from CDT with EKOS is not immediate as thrombolysis requires time, whereas aspiration thrombectomy can achieve rapid thrombus removal and hemodynamic improvement during the procedure. Last but not

![Fig. 5. Example of Angiojet Rheolytic Thrombectomy procedure for acute deep vein thrombosis. A: baseline venogram showing thrombosis of entire left femoro-popliteal vein; B: Angiojet procedure; C: post Angiojet procedure venogram showing complete recanalization of the femoro-popliteal vein.](image-url)

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<th>Risk Category</th>
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<td>Hemodynamic</td>
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<td>Intermediate</td>
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least, aspiration thrombectomy might be more suitable in the patient with high bleeding risk and contraindications to thrombolitics, as it can be performed heparin-free. In particular, the Penumbra Indigo CAT 12 with Lightning intelligent aspiration system using computer-aided clot detection technology might potentially speed up the procedural time and reduce procedure-related blood loss [33].

Endovenous intervention for chronic thromboembolic pulmonary hypertension

CTEPH is one of the most serious chronic complications of acute PE. The incidence of CTEPH was reported to affect 5–7% of patients with acute PE [34,35]. However, with enhanced awareness and screening, the incidence of CTEPH has been shown to increase in recent years [33]. Similar to PTS in DVT, the pathophysiology of CTEPH is the occlusion of the pulmonary artery from the organized thrombus, with additional involvement from pulmonary vascular and right ventricular remodelling [36]. Therefore, besides endovenous intervention, comprehensive background medical therapy for pulmonary hypertension and managements by a multi-disciplinary pulmonary hypertension unit are essential for the care of patients with CTEPH [8].

The gold standard treatment of CTEPH is surgical pulmonary endarterectomy, which although offers the best chance to improve long-term clinical outcomes, is restricted to treatment of occlusions in large main and lobar pulmonary arteries, and is associated with significant perioperative mortality [37–39]. Endovascular balloon pulmonary angioplasty (BPA) has been introduced recently as an alternative to surgical endarterectomy, especially for patients with involvement of more distal and smaller pulmonary arteries and in whom surgical risk is estimated to be high [8,40] (Table 1). BPA involves standard angioplasty procedures using conventional coronary equipment such as guiding catheters, guidewires and monorail balloon. BPA aims to disrupt organized, flow-limiting obstructions to improve pulmonary blood flow. Stenting is generally not encouraged in the exception of stent graft for treatment of vascular perforation of large vessel. Typically, several sessions of BPA are required to produce meaningful clinical improvement, as only 1–2 pulmonary lobes are recommended to be treated each time. Periprocedural complications include pulmonary vascular injury and reperfusion pulmonary oedema, which occurs more frequently in patients with more disease burden and higher baseline pulmonary arterial pressure. Several risk scores such as the PEPSI score have been developed to predict which patients are at a higher risk of developing complications [41,42]. Detailed pre-procedural planning and careful patient selection therefore are important to avoid these serious complications [40]. Comparable clinical outcomes and hemodynamic improvements as in surgical endarterectomy can be expected from successful BPA [43–45].

Conclusions
Venous disease can impart significant morbidity and mortality to patients if left untreated. Significant advancements in endovenous technology have enabled effective treatments of various venous diseases with minimal complications. In selected patients, endovenous intervention can significantly improve clinical outcomes and reduce disease burden.

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Conflict of interest
The authors have no conflict of interest to declare.

Ethical information
Not applicable

References


