Review Article The role of molecular imaging in diagnosis of deep vein thrombosis

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Abstract: Venous thromboembolism (VTE) mostly presenting as deep venous thrombosis (DVT) and pulmonary embolism (PE) affects up to 600,000 individuals in United States each year. Clinical symptoms of VTE are nonspecific and sometimes misleading. Additionally, side effects of available treatment plans for DVT are significant. Therefore, medical imaging plays a crucial role in proper diagnosis and avoidance from over/under diagnosis, which exposes the patient to risk. In addition to conventional structural imaging modalities, such as ultrasonography and computed tomography, molecular imaging with different tracers have been studied for diagnosis of DVT. In this review we will discuss currently available and newly evolving targets and tracers for detection of DVT using molecular imaging methods.

Keywords: FDG-PET/CT, venous thromboembolism, deep vein thrombosis, SPECT, molecular imaging

Introduction

Venous thromboembolism (VTE), mostly presenting as deep vein thrombosis (DVT) and pulmonary embolism (PE), affects approximately 300,000 to 600,000 individuals and 60,000 to 100,000 die of VTE each year in the United States [1-4] more than prostate and breast cancer combined [5]. VTE has a relatively high mortality rate of 6% for DVT cases and 12% of PE cases within the first month of diagnosis [6, 7]. One-third VTE cases are manifested as PE and 2/3 present with DVT alone [4]. Eighty to 90% of pulmonary embolism cases are caused by DVT or a thrombus formed in the pelvis [8]. US healthcare system carries a huge burden for treatment of VTE and its complications, which is estimated to be \$1.5 billion/year [9]. It is very important to correctly diagnose VTE before instituting an intervention, however, currently available diagnostic methods have pitfalls and is sometimes misleading [10].

The established modalities and current gold standards for evaluation of VTE may be inapplicable in some situations. Ultrasonography (US) has replaced contrast venography for the diagnosis of DVT because of availability, performance, elimination of radiation and contrast agents [11]. However, US is dependent on user experience and also could be compromised by mechanical obstacles. US contrast medium is highly allergenic and not suitable for cardiac patients. It is also not applicable for body cavity and non-occlusive thrombi [12, 13]. In patients with involvement of the vasculature below the knee or in the pelvic veins, in asymptomatic patients, and in patients with duplicate veins, US might show false negative results [14-16]. Venography and US can only reflect changes in venous anatomy, which is caused by filling defects and cannot show the metabolic activity of the clot. Since morphologic changes may remain present for years after an episode of DVT, patients with a prior history of DVT represent a challenge to diagnosis because of difficulty in differentiating new clots from residual ones [15, 17]. Up to 11% of CT venograms are insufficient for diagnosis of DVT [10, 18] and are not recommended for the initial assessment of DVT due to invasiveness, technical difficulties and potential complications (e.g., hematoma, allergic reaction to contrast media) [19]. Patients with implanted electronic devices



Figure 1. A schematic view depicting elements of the venous thrombus and binding sites for different radiotracers. 1. FDG taken up by metabolically active inflammatory cells and platelets. 2. Radiolabeled platelets indicating sites of aggregated platelets. 3. GP IIb/IIIa cyclic RGD peptides (Apcitide, DMP 444, Bitistatin) targeting GP IIb/IIIa receptors on activated platelets. 4. TP850 pentapeptide targeting fibrin α chain. 5. 59D8, T2G1, GC4, 64C5 targeting fibrin β chain. 6. Cyclic fibrin binding peptide EP-2104R. 7. DI-80B3 targeting D-domain of the fibrin. 8. Fibronectinbinding domain targeting lysine residue in fibrin. 9. Recombinant tissue plasminogen activatior (rt-PA) binding to C-terminal lysine residue of fibrin.

and intractable claustrophobia or renal failure cannot undergo magnetic resonance imaging (MRI) with contrast media [13].

With the emergence of nuclear medicine methods, new perspectives were opened early on for diagnosis of DVT [20]. Initial trials for diagnosis of DVT using radiolabeled antibodies targeting fibrin, activated platelets, plasminogen, plasmin, factor XIII were not promising due to their long blood circulation time and radioactivity accumulation in the lungs and problems with timing of availability of the epitope which antibody was designed to bind, causing low clot to blood ratios [21-23]. Later on, studies focusing on specific synthetic peptides targeting fibrin and platelet receptors have shown more promising results [15, 22, 24-43], which will be discussed in this review (Figure 1). These new tracers might be able to aid the currently used modalities for detection of DVT.

Here, we will discuss currently available and newly evolving targets and tracers for detection of DVT using molecular imaging methods and evaluate potential of 2-deoxy-2-[¹⁸F]fluoro-D-glucose-positron emission tomography/CT (FDG-PET/CT) as an accurate diagnostic tool for assessment of DVT (**Table 1**). We will also briefly discuss the role of FDG-PET/CT in detection of tumor thrombosis and septic thromboembolism.

Pathophysiology of thrombosis

Since we will focus on agents involved in molecular mechanisms of thrombosis, the complex

cascade of blood coagulation will be reviewed briefly. Hemostasis of blood is a complex mechanism for maintaining blood fluidity and conversion to insoluble gel in sites of vascular injury. Platelets and coagulation proteins are two major forces interacting with each other. In arterial thrombosis, loss of endothelial layer exposes platelets to subendothelial ligands and activates them causing cascade of procoagulant molecules such as factor V, Von Willebrand factor (VWF) and fibrinogen to be released and promotes the flip-flop reaction exposing phosphatidylserine on outer membrane leaflet of platelets, providing surface for generation of thrombin and fibrin deposition [44]. Arterial thrombi are platelet rich and composed of a core of platelets over the vessel injury site and a mesh of fibrin covering platelets [45]. Mechanisms behind venous thrombosis are less clear. Vessel wall injury is not considered the prominent initiating event in venous thrombosis [44, 46]. Two distinct regions are present in venous thrombi, red thrombi consisting of fibrin and trapped red blood cells and white thrombi composed of aggregated platelets [44]. Fibrin rich region attaches the thrombi to the vessel wall and platelet rich regions are attached to the fibrin rich region distally [44, 47, 48]. According to Virchow's triad, which described the pathogenesis of VTE many years ago [49], stasis, endothelial changes and increase in blood thrombogenicity contribute to VTE. Additional factors are also described which include inflammation and abnormalities of fibrinolytic mechanisms [50]. Many VTE

Binding site	Tracer	Modality	Study, Publication year	Study population (number)	Reference
Platelet	¹¹¹ In labeled platelet	Planar Scintigraphy	Thakur et al., 1976; Knight et al., 1978,	Animal/Human (multiple studies)	[98, 99]
Platelet, GP IIb/IIIa receptor	Cyclic RGD Peptide (99mTc-Apcitide (P280))	Planar Scintigraphy	Dunzinger et al., 2008; Taillefer et al., 2000	Human (n=19); Human (n=280, Phase III)	[33, 39]
Platelet, GP IIb/IIIa receptor	Cyclic RGD Peptide (^{99m} Tc-DMP 444, ^{99m} Tc-P4 DMP 444)	Planar Scintigraphy	Fang et al., 2011; Klem et al., 2000	Animal; Human (n=11)	[22, 41]
Platelet, GP IIb/IIIa receptor	Cyclic RGD Peptide (99mTc-Bitistatin)	Planar Scintigraphy	Knight et al., 2000; Knight et al., 2007	Animal; Human (n=4, Phase I)	[34, 119]
Platelet, Thrombospondin receptor	99mTc-TP 1201, 99mTc-TP 1301	Planar Scintigraphy	Pallela et al., 1999	Animal	[151]
Fibrin, Alpha chain	^{99m} Tc-TP850	Planar Scintigraphy	Aruva et al., 2006; Thakur et al., 2000	Animal	[36, 75]
Fibrin, Beta Chain	¹¹¹ In-59D8, ¹¹¹ In-T2G1, ¹¹¹ In-GC4, ¹¹¹ In-64C5	Planar Scintigraphy	Morris et al., 1997; Alavi et al., 1990; Jung et al., 1989; Lusiani et al., 1989; DeFaucal et al., 1991; Stratton et al., 1994,	Animal/Human (multiple studies)	[64, 65, 67, 69, 74, 79, 94]
Fibrin	Cyclic fibrin binding peptide (EP-2104R)	MRI	Vymazal et al., 2009; Spuentrup et al., 2008	Human (n=14, n=10)	[32, 85]
Fibrin	EP-2104R	NIRF	Hara et al., 2012	Animal	[68]
Fibrin	¹¹¹ In-EP-2104R (FibPep)	SPECT	Starmans et al., 2013	Animal	[25, 26]
Fibrin	⁶⁴ Cu-DOTA-FBP EP-2104R	PET/CT	Cieskienski et al., 2013	Animal	[27]
Fibrin	EP-2104R based dual PET/MR probe	PET/MR	Uppal et al., 2011	Animal	[87]
D-Domain	Anti D-dimer ^{99m} Tc-DI-80B3 Fab' fragment (ThromboView®)	Planar Scintigraphy	Douketis et al., 2012	Human (n=82, Phase II)	[24]
D-Domain	99mTc-DI-DD3B6/22-80B3	SPECT	Macfarlane et al., 2009	Human (Phase I, n=21)	[31]
D-Domain	¹¹¹ In-anti D-dimer	Planar Scintigraphy	Morris et al., 2004	Animal	[72]
Region 102-10	$^{89}\text{Zr-}102\text{-}10$ (anti-Bß and anti-y mAb)	PET/CT	Hisada et al., 2013	Animal	[82]
Factor XIII	CLIO-FXIII	NIRF/MRI	McCarthy et al., 2009, Tung et al., 2003	Animal	[38, 97]
Fibronectin	¹¹¹ In-FBD	Planar Scintigraphy	Rosenthall et al., 1995	Human (n=62)	[95]
Plasmin	¹³¹ I-Plasminogen, ¹²³ I-Plasminogen	Planar Scintigraphy	Harwig et al., 1976	Animal	[128]
Plasmin	^{99m} Tc-Plasmin	Planar Scintigraphy	Dahlborn et al., 1984	Animal	[121]
Tissue plasminogen activator	^{99m} Tc-rt-PA	Planar Scintigraphy	Brighton et al., 2007	Human (n=74)	[35]
Tissue plasminogen activator	¹²³ I-t-PA	Planar Scintigraphy	De Bruyn et al., 1995	Animal	[152]
Active inflammatory cells	¹⁸ F-FDG	PET/CT	Rondina et al., 2012	Human (n=36)	[12]
Active inflammatory cells	¹⁸ F-FDG	PET/CT	Hess et al., 2014	Human (n=15)	[137]

 Table 1. List of targets and tracers studied for detection of venous thrombosis

patients fulfill most or all of Virchow's triad [45, 51, 52].

Targeting fibrinogen, fibrin and their derivatives

Fibrinogen is a soluble glycoprotein circulating in blood consisting of two outer D domains connected by a coiled segment to its central E domain. Fibrinogen contains two sets of three polypeptide chains: alpha, beta and gamma. Thrombin mediates cleavage of fibrinopeptides A and B from alpha and beta chains of fibrinogen, producing fibrin monomers, which polymerize and form fibrin fibers and subsequent insoluble fibrin network, making the scaffold for thrombus [53, 54]. Fibrin and its related proteins have been a main target for investigations related to VTE in the literature which will be discussed in the following paragraphs.

Traditional anti-fibrin antibodies

Fibrinogen labeled with ¹²⁵I was popular in the early 1990s but abandoned because of low sensitivity, low specificity and the need for a long delay from injection to imaging [21, 55-57]. Polyclonal antibodies against fibrin were labeled with ¹³¹I, ¹¹¹In and used for detection of venous thrombi. However, the problem of long half-life and time consuming imaging was still present [47, 58]. Later on, production of monoclonal antibodies, increased the specificity of fibrin detection and techniques of antibody fragmentation helped faster clearance from blood. These factors altogether enabled applicability of radiolabels with shorter half-life like ^{99m}Tc [47, 59-63].

Fibrin beta chain antibodies

Fibrin has been a target for various studies focusing on imaging of thrombus and different types of antibodies have been introduced to the literature [20, 22, 25, 27, 32, 36, 57, 60, 61, 63-76]. Antifibrin antibodies 59D8 [77] and T2G1 [59, 78] bind to a 7 amino acid sequence on beta chain of human fibrin with a binding site specific for cross-linked fibrin undergoing active thrombosis [47]. Preliminary results from human studies of ¹¹¹In labeled 59D8 showed a combined sensitivity and specificity of 87% up to 4 hours post injection compared to venography in total of 159 patients [58, 64, 65, 67, 69, 79]. However, as mentioned above, the prob-

lem of blood clearance and half-life of tracer still persisted. The preliminary results from a study on ^{99m}Tc labeled T2G1 in DVT patients showed an overall sensitivity of 80% and 94% for proximal DVT [58, 65]. It has been hypothesized that heparin might interfere with antibody binding to fibrin [58, 65]. It has been shown that GC4, which is a monoclonal antibody against fragment D of fibrin, has tendency to old thrombi which has greater uptake during heparinization compared to T2G1 [73]. Another example of fibrin specific molecules is fragment E, a plasmin degradation product from crosslinked fibrin [80]. ¹¹¹In labeled monoclonal antibody 64C5 specific for the beta-chain was used for canine (n = 6) pulmonary emboli [81].

The published human studies for detection of thrombi using fibrin antibodies [65-67, 69] have shown acceptable sensitivity and specificity. For example, Alavi et al. [64, 65] in 1990 used ¹¹¹In labeled antifibrin antibody in patients suspected of VTE with a sensitivity of 97% in 33 patients versus venography. Jung et al. [69] showed sensitivity and specificity of 84% and 81%, respectively. However, the patient group had a high pretest probability for DVT. The study of De faucal et al. had a sensitivity of 85% and specificity of 100% in 10 patients [67].

Bautovich [66] used another anti-fibrin antibody named DD3B6/22 and noted a sensitivity of 100% in 20 patients. However, none of these studies could optimally bind thrombi during anti-coagulation [72].

Hisada et al. [82] have recently discovered an uncovered region (named 102-10) in fibrin clot with specificity for insoluble fibrin against fibrinogen, soluble fibrin and D-dimer. They investigated its applicability in clot detection in microhemorrhages of tumoral masses in mice by designing monoclonal antibodies (mAb) against elements of this region and radiolabeling them with ⁸⁹Zr (⁸⁹Zr labeled 102-10) and subsequent immunohistochemical assessment. They concluded that their newly developed antibodies against insoluble fibrin mAbs are feasible for detection of high-grade and aggressive tumors.

Cyclic fibrin-binding peptides

Cyclic fibrin binding peptide EP-2104R, composed of a fibrin-binding motif and four Gd-1,4,7,10-tetraazacyclododecane-1,4,7,10-

tetraacetic acid (DOTA) moieties, has been studied for MRI visualization of fibrin deposition in PE, atherosclerosis, coronary and carotid artery thrombosis [32, 83-86]. EP-2104R has successfully passed phase II clinical trials [32, 83-86]. A similar structure introduced by Starmans et al. [26], ¹¹¹In labeled fibrin-binding peptide named FibPep, containing cyclic fibrin binding motif has been studied in vivo using mice and in vitro. They showed enhanced binding compared to control tracer to fibrin and blood clots in vitro with 100 fold higher affinity. In vivo studies showed clear visualization of the thrombi and rapid blood clearance making it feasible for sensitive detection of thrombi using SPECT. Further studies are needed to investigate the potentials of this compound in thrombosis, atherosclerosis and cancer research. Starmans et al. in a newer study [25], introduced EPep, ¹¹¹In-labeled fibrin binding peptide which incorporated EP-2104R's fibrin binding site and compared it with FibPep. Both peptides were approximately similar in metabolic stability and affinity.

Uppal et al. [87] used a dual modality PET/MR probe EP-2104R on rat arterial thrombus model. They observed thrombus enhancement in all animals at both MR and PET after injection of probe.

Ciesienski et al. [27] designed three new simplified fibrin-targeted PET probes based on EP-2104R and two other similar sequences previously shown to bind to fibrin with high affinity and conjugated them to ⁶⁴Cu-DOTA [84, 88]. They used PET imaging in rat models of arterial thrombosis. Two of the probes showed enhanced metabolic stability in vivo with fourfold thrombus to background ratio and accurate detection of arterial thrombus and imaging efficacy in hybrid MR-PET imaging. However, these probes have a long residual activity in blood even after 120 minutes, therefore future work is needed to modify these probes.

Ay et al. [89] have recently introduced a fibrinbinding peptide 7 (FBP7) for detection of thrombosis with promising results in animal models of arterial thrombosis. Although their model was designed for occlusive and non-occlusive arterial thrombi in the carotid arteries, this ⁶⁴Cu labeled compound might be useful in venous thrombosis as well. Hara et al. [68] investigated the avidity and specificity of a newly synthesized near infrared fluorescence (NIRF) thrombus imaging agent based on already known EP-2104R, namely FTP11-Cy7 in acute and sub-acute murine DVT in vivo using high-resolution intra-vital fluorescence microscopy and noninvasive integrated fluorescence molecular tomography-CT. They found FTP11-Cy7 binds specifically and avidly to thrombus with high target to background ratios enabling non-invasive and sensitive detection of acute and sub-acute murine DVT.

Fibrin alpha chain: TP850

Laudano and Doolittle introduced a tripeptide corresponding to alpha chain of fibrin with inhibitory properties of fibrin polymerization [90]. Kawasaki et al. [91] prepared additional analogs with more potent activity against thrombin clots. Thakur et al. [75] have investigated ^{99m}Tc-TP 850, a fibrin alpha chain N-terminal pentapeptide similar to mentioned peptide that binds to C terminal of gamma chain of fibrin for detection of chronic and acute DVT or PE in animal models of DVT and PE. The resulting images showed stability in vivo and in vitro, the tracer cleared rapidly from blood and was able to delineate experimental DVT and PE.

Aruva et al. [36] imaged thromboembolism with TP 850 in swine models of DVT and PE. They measured modest affinity for ^{99m}Tc-TP 850 with rapid blood clearance and high DVT and PE uptake.

D-dimer (thromboview)

The D-domains of fibrin connect covalently with unique antigenic sites which antibodies are made for binding to these structures [31, 76, 92, 93]. Murine monoclonal antibodies (DI-DD-3B6/22) were the first class of these antibodies [31, 66]. The next generation with modified structure and optimized efficacy by replacing murine specific sequences not involved in antigen detection with human equivalent was DI-DD3B6/22-80B3 Fab' fragments [71, 72]. DI-DD3B6/22-80B3 has unique properties such as anatomical localization of clot, differentiating new and old lesions in patients with suspected recurrence, elimination of intravenous contrast dye. Furthermore, it has some advantages over US by having the ability to identify non-occlusive proximal DVT or distal

Role of molecular imaging in DVT diagnosis



DVT and obese or edematous patients in whom US may be difficult to interpret [24] (See **Figure 2**).

Morris et al. [71] used ^{99m}Tc labeled deimmunized antifibrin Fab' fragments and SPECT to detect DVT and PE in 5 dogs with induced DVT and subsequent embolization and were able to visualize all PEs and DVTs with mass of 0.4 g or greater. PEs (0.48 \pm 0.09 g) were intensely radiolabeled, yielding clot/blood radioactivity ratios of 22.8 \pm 5.6. DVTs (0.45 \pm 0.31 g) also had high clot/blood ratios (11.7 \pm 2.6). Imaging was done at 4 hours after injection. However, the study was not able to detect sub-segmental emboli in dogs. Morris et al. [94] also compared imaging of DVT during anticoagulation by ¹¹¹In labeled antibodies against D-Dimer, fibrin beta chain in dogs by gamma scan. D-dimer was 100% sensitive but anti-beta was only 60% sensitive. The clot/ blood ratio was 24.5 \pm 2.8 in the anti-D-dimer group, but only 7.8 \pm 2.0 in the anti-beta group.

In phase I of a trial to image DVT using radiolabeled anti D-Dimer fab' fragment, Macfarlane et al. [31] have evaluated ^{99m}Tc-DI-80B3 imaging of 26 patients with acute DVT for safety. Douketis et al. [24] did the multicenter phase II prospective cohort trial on 82 patients to investigate diagnostic accuracy and safety of ^{99m}Tc-DI-80B3 in DVT patients. They found no serious adverse effect, 84% sensitivity, and 97% specificity for proximal DVT and lower accuracy for distal DVT. They could not comment on recurrent DVT due to lack of adequate number of patients.

Fibronectin

Fibronectin is one of the most abundantly found proteins in plasma and is involved in cross-linking of fibrin dimers with multifunctional adhesive properties [15]. The ^{99m}Tc-FBD contains part of fibronectin which is responsible for directing it to blood clots.

Initial pilot study [95] was done using ¹¹¹In-FBD after 18 to 24 hours of injection of radiotracer which showed preliminary encouraging results, further pilot studies by Thaillefer with ^{99m}Tc-FBD showed sensitivity of 80% by considering equivocal as normal and better sensitivity in proximal DVT (87% to 97%) than distal DVT (56% to 78%) [15, 95].

Factor XIII

Clotting factor XIII is an endogenous protein with ability to crosslink polymerized fibrin molecules together and adding stability to the forming thrombus. Since factor XIII crosslinks to fibrin, it is a good target for detecting active thrombosis.

Preliminary studies on factor XIII showed relative similarity in ability to achieve an acceptable thrombus-to-blood ratio [47]. However, further studies were halted presumably due to its low blood clearance and large molecular weight. In 2003 a novel, thrombosis-specific diagnostic probe based on the factor XIII transglutaminase activity and previously identified peptide substrates with near-infrared fluorescence probe and gadolinium (Gd) chelating MR probe became available [38]. McCarthy et al. [96, 97] have also synthesized efficient multimodal nanoagents targeting activated factor XIII.

Targeting platelet and its receptors

Radiolabeled platelet

Since the late 1970s, ¹¹¹In labeled platelets have provided physiologic data of platelet for therapeutic decisions and assessment of atherosclerosis, angioplasty, vascular grafts and venous thrombosis and it was once the only FDA approved method of functional imaging of thrombus formation [98, 99]. However, this method was time-consuming requiring up to 24 hours of imaging delay [74, 100]. Signal-tonoise ratio was also low, and there was a lack of documentation of underlying pathological condition [101]. Therefore, methods that are more rapid were needed.

Cyclic Arg-Gly-Asp (RGD) peptides: GPIIB/IIIA platelet receptor antibody

DVT can be detected by targeting membrane glycoproteins IIb/IIIa (GPIIb/IIIa), which are expressed on platelets to form platelet bridges, found predominantly in thrombi. It is estimated that activated platelets present more than 80,000 GP IIb/IIIa receptors on their membrane [29, 102].

Short synthetic peptides containing analogues of Arg-Gly-Asp (RGD) have been extensively tested for their ability to image thrombosis and tumors [30, 103-107]. The problem of long circulation time of radiolabeled antibodies can be alleviated using small peptides that are cleared quickly from the blood circulation [22, 33, 36, 39-43, 108-116]. These peptides showed rapid clearance from blood, but their tissue-to-background contrast was not satisfactory [110, 117]. Zhou et al. [30] have extensively reviewed cyclic RGD peptides and their applications. Here are examples of these peptides, which have been studied for imaging thrombosis.

Apcitide (AcuTec): Apcitide is a synthetic RGDmimicking polypeptide, which binds to glycoprotein IIb/IIIa receptors on activated platelets. Apcitide was approved for clinical use in 1998 and has since been studied for detection of acute DVT and PE [30, 43, 118].

Dunzinger et al. [33] have studied patients with DVT and PE using ^{99m}Tc-apcitide to detect thrombosis. The results of 19 patients were compared to ultrasonography and/or phlebography. The results showed acute clot formation in 14 out of 16 patients with DVT up to 17 days after onset of clinical symptoms. Only one out of six patients with imaging proven segmental or sub-segmental PE was detected by ^{99m}Tcapcitide. Apcitide had a sensitivity of 87% and specificity of 100% for acute DVT, however the sensitivity for PE was poor.

Thaillefer et al. [39] in their Phase III multicenter trial for detection of thromboembolic disease compared ^{99m}Tc-apcitide scintigraphy with contrast venography in 280 patients within 10 days of onset of signs and symptoms of acute DVT or 10 days of surgery associated with high risk of DVT. Blinded reading of ^{99m}Tcapcitide scintigraphy and contrast venography had a sensitivity of 73.4%, specificity of 67.5%, and agreement of 69.1%. The study included patients with history of previous DVT, which might confound the venography results. In a subset of patients without previous DVT episodes, sensitivity, specificity and agreement were 90.6%, 83.9% and 87.3% respectively. Thus apcitide could be used as a sensitive imaging for acute DVT. Same lead author in another study compared ^{99m}Tc-apcitide at multiple time points with contrast venography. When images at multiple time points were analyzed together, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio rose to 85.4%, 88.3%, 7.38, and 0.154, respectively [37, 113].

Bates et al. [108] have used radiolabeled peptide apcitide on 38 patients with newly diagnosed DVT, and 40 patients with previous DVT, post thrombotic symptoms, and ultrasonography abnormalities. Sensitivity of ^{99m}Tc-apcitide was 92% for two expert readers and specificity was 82% and 90%, respectively. However, they reported lower accuracy and inter-reader agreement for inexperienced physicians.

DMP 444: Another peptide targeting activated platelets as a GP IIb/IIIa receptor antagonist is ^{99m}Tc-DMP444 [42]. It actively incorporates into arterial [111, 116] and venous thrombi in DVT and PE. It has also been used in imaging infective endocarditis [101, 109, 115].

Kelm et al. [41] reported detection of DVT with ^{99m}Tc labeled DMP 444 in 10 patients with clinical suspicion of DVT confirmed with US and D-Dimer. All patients underwent planar imaging, and no significant adverse effect was noted. Eight patients demonstrated areas of increased activity with correlation to ultrasonographic findings. This preliminary study showed safety and potential value of DMP 444 in future studies.

Anti GP Illa: Ji et al. [29] have investigated human and mouse/human chimeric versions of monoclonal antibody against platelet GPIIIa, SZ21, and chSZ21, respectively in canine PE and DVT models. Their results showed focal uptake on planar images as early as after 30 minutes and clearer uptakes after 3 hours. Lesion-to-background ratio was 12.8 for PE/ lung and 7.2 for DVT/blood and 117 for DVT/ muscle.

Bitistatin: Bitistatin is an 83 amino acid polypeptide isolated from viper venom, which binds avidly to GPIIb/IIIa receptor of the platelets. Knight et al. labeled bitistatin with ^{99m}Tc and assessed the ability of bitistatin for detection of PE and DVT. In their preclinical model, the uptake in thrombus and embolus was higher than other thrombus targeting tracers 0.5 to 4 h after injection [119]. Subsequently, recombinant version of bitistatin replaced the native one [34] and in phase I clinical trial showed safety and was able to bind to circulating platelets. Future studies are needed to elucidate the role of bitistatin in clinic.

As a summary, various peptides and antibodies are being developed and examined in animal and human studies targeting receptors on the activated platelets. However, most of these agents are in either pre-clinical setting or phase I clinical trials. Therefore, more time is needed to be able to make an accurate comparison among these agents.

Targeting plasmin and its derivatives

Fibrinolytic system associated with hemostasis consists of two types of proteolytic enzymes: plasminogen activator and plasmin. Plasminogen activator has two types: tissue-type plasminogen activator (TPA) and urokinase-type plasminogen activator; both synthesized in vascular endothelial cells and released to bloodstream. When fibrin clots form, circulating plasminogen and TPA bind to fibrin. Then, TPA activates fibrin-bound plasminogen to plasmin, which in turn degrades in situ fibrin [120]. This close relationship with thrombus formation and degradation makes plasmin and TPA a good target for imaging thrombus.

Plasmin

Several studies have evaluated DVT by gamma camera detection of ^{99m}Tc-Plasmin [121-127] and compared with phlebography. Although their results showed relatively favorable sensitivity, the specificity, predictive values and accuracy were not satisfactory for DVT diagno-



Figure 3. New deep vein thrombosis in right leg. FDG MIP image (A), axial PET (B), and axial PET/CT (C) show high metabolic activity (red arrows) in a dilated vein consistent with a fresh new clot.

sis, specifically after hip replacement surgery [124].

Plasminogen

Harwig et al. [128] investigated radio iodinated plasminogen for localization of canine preformed thrombi. Two days after thrombus formation, radiolabeled plasminogen was injected and thrombus-to-blood activity ratio of 7.8 \pm 2.4 was obtained. Even 6 days old thrombi were visible in 80% of cases. However there was variability in thrombus weight and thrombus blood ratio in 1-day-old thrombi, which might have been caused by plasminogen release accompanying thrombus retraction.

Tissue-type plasminogen activator (TPA)

Brighton et al. [35] examined relative uptake of ^{99m}Tc-rt-PA in acute DVT over first 30 days after diagnosis. Plasminogen activation site of rt-PA undergoes inactivation but fibrin binding is retained. As the thrombus ages fewer fibrin sites will be available for ^{99m}Tc-rt-PA binding. They studied 74 patients with acute symptomatic DVT who underwent ultrasound and ^{99m}Tc-rt-PA imaging and found 72% uptake on day 7 and 0% uptake after 30 days. They concluded

^{99m}Tc-rt-PA could distinguish new from old thrombus.

Targeting inflammatory cells involved in VTE

The role of $^{\rm 18}{\rm F}\text{-}{\rm FDG}\text{-}{\rm PET}/{\rm CT}$ in detection and assessment of DVT

¹⁸F-FDG is an analog of glucose, which is the major source of energy and therefore taken up by various cells in the body, including tumoral cells and the ones involved in inflammation and coagulation such as macrophages, endothelial cells and lymphocytes. It is suggested the process of VTE is closely related to inflammation and expression of cell adhesion molecules and leukocyte adhesion and thrombosis and subsequent uptake of FDG in thrombosed areas [12, 129]. Incidental findings of thrombosis detected by FDG-PET/CT in various malignant and non-malignant diseases including hepatic lymphoma, colon cancer, pancreatic neuroendocrine tumor, alcoholic cirrhosis, renal cell carcinoma, have been reported in the literature [130-136], mainly considered as tumor thrombi.

Ability of FDG-PET/CT for recurrent and new VTE differentiation, detection of malignancy



Figure 4. Suspected recurrence of deep vein thrombosis in right leg. Axial CT (A) shows a dilated vein with no metabolic activity in combined axial PET/CT (B, red arrows) consistent with inactive old changes; no new clot.

secondary to VTE, VTE and tumor thrombosis discrimination has been reviewed previously [10]. However applicability of FDG-PET/CT as an all in one imaging method and use in new patient categories and non proximal lower extremity areas (like calf, pelvic area, upper extremity, sagittal sinus thrombosis and PE) is still unclear and further studies are needed to clarify that.

Rondina et al. [12] prospectively studied 12 patients with confirmed proximal thrombosis of the lower limb using FDG-PET/CT and detected thrombosis with sensitivity of 87.5-100% and specificity of 87.5-100% varying with two thresholds for maximum standard uptake value (SUVmax) (1.64 and 1.49). There was a negative correlation between maximum metabolic activity in thrombosed veins (SUVmax) and time from DVT symptom onset suggesting a steady decrease over time, a prerequisite for differentiation between old and new thrombi, and for response evaluation.

In another study, Hess et al. [137] prospectively examined 15 patients with suspected DVT and/ or PE with subsequent FDG-PET/CT less than 24 hours after the diagnosis had been confirmed or ruled out based on local guidelines. Images were interpreted visually, i.e. DVT/PE was considered present with focal or linear increased FDG uptake within the veins/pulmonary vasculature, and absent with no pathologic FDG uptake. They found FDG-PET/CT able to correctly diagnose or rule out acute DVT in all patients (**Figures 3, 4**), whereas PE cases were less favorable with only 2 out of 6 PE patients being positive on FDG-PET/CT.

Based on results of abovementioned studies and these preliminary results of volumetric FDG-PET/CT parameters, FDG-PET/CT biomarkers appear to be promising for detection of deep vein thrombosis and other VTE subcategories. However, confounding factors contributing to false positive results, such as co-existing inflammation or infection should be considered while interpreting FDG-PET/CT for diagnosis of DVT [138, 139].

Gynecologic thrombotic disorders such as VTE in pregnancy pose a

major diagnostic challenge since no test diagnostic test has shown adequate accuracy with acceptable margin of safety [140, 141]. DVT in pregnancy usually occurs in proximal veins and therefore, currently accepted first test in patients with clinical suspicion of DVT is compression ultrasonography but based on represented data, the test results appear suboptimal [140]. One of the advantages of molecular imaging based technique is its ability to visualize clots in the venous system in the anatomical regions such as pelvis, which is not feasible by other modalities. Since pelvis is considered a source of clot formation and PE, molecular imaging and specifically FDG-PET might be a useful modality for detection of clots in this region.

Tumor thrombosis and FDG-PET/CT

In most patient studies reported in the literature about VTE and FDG-PET/CT, the thrombus was found incidentally or retrospectively in patients investigated because of underlying malignancy, and thus, presented data on the differential diagnosis between "benign" (bland) and "malignant" (tumor) thrombi.



Figure 5. The FDG-PET image above demonstrates relatively intense uptake of FDG in superior vena cava of an 8-year-old patient with neuroendocrine malignancy, which was interpreted to represent active thrombotic lesion in this location. Metastatic uptake in the cervical lymph nodes on the left side is also visible.

Davidson et al. [142] retrospectively evaluated 11 patients with suspected tumor thrombosis. FDG-PET/CT scans were considered positive if they demonstrated focal or linear uptake in the involved vessel. Eight occult tumor thromboses were found by FDG-PET/CT, in patients with gastrointestinal, renal, head and neck malignancies or lymphoma. Three thrombotic lesions were PET negative and these were due to VTE or leiomyomatosis. Thus in this study, FDG-PET/CT could distinguish benign from malignant thrombosis in all patients.

Lee et al. [143] have retrospectively evaluated FDG-PET/CT for the detection of tumor thrombosis. They reviewed 24 sites of thromboembolism in 15 patients with contrast enhanced CT scan, metabolic activity was measured by drawing regions of interest (ROI) and recording SUVmax of the site of thrombosis. ROC analysis was done to determine cutoff point of SUVmax for detection of tumor thrombosis. There was a significant difference between tumor and bland thombus SUVmax (P<0.005) and a cutoff of 2.25 with sensitivity of 78% and specificity of 100% was determined for SUVmax to differentiate tumor thrombus and bland thrombus.

Sharma et al. [144] retrospectively reviewed FDG-PET/CT of patients with known malignancy and FDG avid thrombosis. SUVmax was measured for blood pool, tumor, and thrombus. Average SUVmax in benign thrombosis groups was 3.2 and 6 in tumor thrombosis group with a significant difference (P=0.013). ROC analysis showed a cut-off SUVmax of 3.63 (71.4% Sensitivity and 90% Specificity) for differentiation of benign and malignant thromboembolism.

Rondina et al. [145] evaluated FDG-PET/CT as a comprehensive screening strategy for occult malignancy. In their pilot study they prospectively investigated 40 patients with unprovoked VTE by use of FDG-PET/CT for detection of occult malignancy. Patients underwent whole body FDG-PET/CT and followed for two years. In 62.5% of patients FDG-PET/CT identified abnormal findings requiring additional evaluations. In this pilot study, occult malignancy was present in only one patient, and FDG-PET/CT was able to rule out malignancy in the remainder.

Callejas et al. [146] in their retrospective survival study of 1331 cancer patients who underwent FDG-PET/CT, detected VTE in 19 patients. Incidental VTE detected by PET-CT was associated with poor survival independently with a hazard ratio of 2.03.

Ravina et al. [147] in another study from our center retrospectively reviewed all FDG-PET/CT scans of oncology cases during a 5 year period and found 21 patients with tumor thrombosis. Average SUVmax of the primary tumors was



Figure 6. A: A 77-year-old female patient presented with Staphylococcus aureus bacteremia presumed to originate from a peripherally inserted central catheter. The catheter had been removed and the patient underwent FDG PET/ CT to establish the extent of disease. Maximum intensity projection image showed unexpected FDG accumulation in the left brachial vein proximal to the removed catheter (green arrow) and in the right lung (red arrows). B, C: Transaxial image of FDG-avid left brachial vein (green arrow). Corresponding CT image revealed stranding in surrounding fat suggestive of inflammation. Subsequent ultrasound confirmed deep venous thrombosis (DVT) of the left brachial vein. D, E: FDG PET showed intense FDG uptake peripherally in the parenchyma of the right lung with barely visible findings on CT (red arrows). Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Clinical Nuclear Medicine [150], copyright (2013).

10.3 and average SUVmax of thrombi was 7.85. The results from this study were in line with other studies regarding usefulness of FDG-PET/CT in tumor thrombosis, and the authors suggested that SUVmax and patterns of FDG uptake can be helpful for differentiating bland thrombus from tumor thrombus in oncological patients (**Figure 5**).

In another unpublished study, we investigated FDG-PET/CT evidence of VTE among cancer patients with clinical VTE diagnosis. In 10 multiple myeloma patients sequential FDG-PET/CT scans before and after VTE diagnosis were reviewed. In 9 out of 10 cases, VTE associated FDG uptake was found at the time of the clinical VTE diagnosis as well as in all FDG-PET/CT performed prior to the clinical VTE diagnosis. Thus, FDG-PET/CT appears to be sensitive for early detection of VTE processes, even in presymptomatic patients.

Septic thrombophlebitis and FDG-PET/CT

Miceli et al. [148] evaluated the role of FDG-PET/CT in diagnosis and management of septic deep thrombophlebitis. They prospectively observed patients with cancer and suspected septic thrombophlebitis and retrospectively reviewed patients with cancer and DVT using FDG-PET/CT. They found a strong uptake in septic thrombophlebitis patients while none of 27 DVT cases had increased FDG uptake. FDG PET was also able to detect central vein septic thrombophlebitis in five patients and caused change in management, while other modalities such as duplex scan and venography were less helpful.

Bleeker-Rovers et al. [149] reported a case of septic thrombophlebitis in portal vein in a 73-year-old man with fever of unknown origin diagnosed by FDG PET. We have also previously reported the incidental detection of septic thrombophlebitis (both DVT and PE) in a patient with bacteraemia in which the diagnosis of VTE was not considered until the FDG-PET/CT scan was done [150] (**Figure 6**).

These studies show FDG-PET/CT is able to diagnose septic thrombophlebitis, especially in hard to reach areas and in patients with unsuspected VTE/septic thrombophlebitis.

Summary and prospective on future imaging techniques for suspected vte

In this review, we have described in great detail imaging techniques that have been employed for detecting clots in the venous system as an important health care issue worldwide. Recent efforts in establishing and optimizing molecular imaging probes that target specific ingredients in the blood clots, opened new horizons for detection of thrombus and overcoming shortcomings of the existing techniques. Examples of these targets are GP IIb/IIIa cyclic RGD peptides and cyclic fibrin binding peptides. Apcitide is the only FDA approved agent among these tracers, which is in phase III multicenter study for DVT. Further studies using other modalities such as PET are suggested to evaluate the role of Apcitide in detection of DVT. Another recently introduced agent investigated in multimodality MRI/PET/SPECT/NIRF studies is EP-2104R. However, only the MR modality has proceeded to human feasibility studies with positive results. Anti D-dimer DI-80B3 Fab' fragment (Thromboview) is another newly introduced agent which has shown favorable sensitivity and specificity for detection of suspected DVT and acute PE.

FDG-PET/CT has been able to detect thrombosis, mainly in the venous system anywhere in the body in patients with suspected DVT. Preliminary data suggest an acceptable sensitivity in the early, even in pre-symptomatic patients. It can also differentiate acute from chronic thrombi that are no longer active and eliminate the need for unnecessary treatment. Furthermore, accurate quantification with FDG-PET/CT allows monitoring response to treatment. Although molecular imaging is not likely to replace established methods of detection of DVT as a first line modality in the near future it is useful in certain clinical settings. FDG-PET/ CT might be a good candidate for aiding diagnosis of DVT because of the limited value of conventional structural imaging modalities. For example, patients with renal disease with contraindication for contrast-enhanced studies might benefit from this modality.

We believe current imaging techniques including radiologic modalities as well as non-PET based approaches that have been described in the literature suffer from certain deficiencies. This is particularly true when we wish to distinguish acute from chronic disease. Therefore, we believe FGD-PET might play a role in detecting thrombosis in the venous system in some clinical settings. Other tracers might be applicable in the future.

At this juncture, FDG-PET imaging appears very promising for suspected VTE and therefore promises a potential role in managing this common disorder. We hope that soon a multicentric trial, sponsored by the National Institute of Health (NIH) or American College of Radiology Imaging Network (ACRIN) will determine the definitive role of FDG-PET imaging in this setting and this eventually will lead to routine use of FDG-PET as an effective method in this common and potentially fatal disease.

Disclosure of conflict of interest

The authors have declared that no competing interest exists.

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