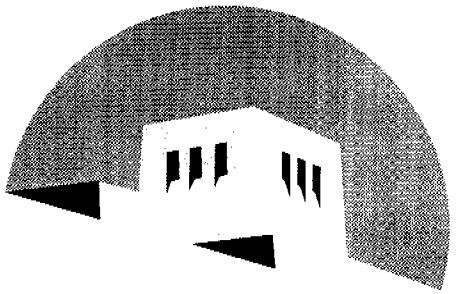

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An Update on the Detection of Deep Vein Thrombosis

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AN UPDATE ON THE DETECTION OF DEEP VEIN THROMBOSIS

STATEMENT OF OBJECTIVES

The purpose of this lesson is to provide a general review of thrombus formation and an overview of techniques for the detection of deep vein thrombosis (DVT). Specifically, this unit will review the potential problems associated with thrombus formation and difficulties that may arise in achieving an accurate diagnosis. It also compares and contrasts established detection techniques with the use of recently approved radiopharmaceutical agents in the diagnosis and localization of DVT.

Upon completion of this continuing education unit, the reader should be able to:

1. Discuss the etiology of thrombus formation.
2. Describe the relationship between DVT and pulmonary embolism.
3. Discuss signs and symptoms of DVT.
4. Discuss the rationale used in the development of medical imaging techniques for thrombus localization.
5. Outline the advantages and disadvantages of contrast venography.
6. Describe the role of impedance plethysmography in the detection of thrombosis.
7. Discuss the principle of compression ultrasound in detecting DVT.
8. Summarize the role of magnetic resonance imaging in the detection of DVT.
9. Discuss the pharmacoeconomic impact of radiopharmaceutical agents in the detection of DVT.

COURSE OUTLINE

I. INTRODUCTION

II. ETIOLOGY
- A. Trauma
- B. Venous Stasis
- C. Hypercoagulopathy

III THROMBUS EVENTS

IV. PROPERTIES OF AN IDEAL DVT DETECTION PROCEDURE

V. DETECTION TECHNIQUES
- A. Contrast Venography
- B. Impedance Plethysmography
- C. Ultrasound
- D. Magnetic Resonance Imaging

VI. NUCLEAR MEDICINE IMAGING TECHNIQUES
- A. Radionuclide Venography
- B. Platelet Scintigraphy
- C. Fibrinogen Uptake and Fibrinogen Scintigraphy
- D. Immunoscintigraphy
  1. Monoclonal Antibodies
  2. Synthetic Peptides
- E. Disintegrins
- F. Recombinant Tissue Plasminogen Activator

V. SUMMARY

AN UPDATE ON THE DETECTION OF DEEP VEIN THROMBOSIS

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INTRODUCTION

Thrombosis is the formation, development or existence of a blood clot or thrombus within the vascular system. This can be a life-saving process when it occurs during a hemorrhage. However, it becomes a life-threatening event when it occurs at any other time because the clot may occlude a vessel and stop the blood supply to an organ or other body part. The thrombus, if detached, becomes an embolus and may occlude a vessel at some distance from the original site (e.g., a clot formed in the leg may break off and travel to the lungs causing a pulmonary embolus).

The venous system, especially in the deep veins of the lower limbs, is the most common site of thrombosis, due to the relatively slow blood flow. The thrombus formed in slow-moving blood is comprised of a layer of platelet aggregates alternating with a fibrin network containing leukocytes and red blood cells.[1]

Although deep vein thrombosis (DVT) is a common clinical event, it remains a difficult diagnostic problem. The diagnosis and prompt treatment of DVT is of notable importance in the prevention of pulmonary embolism, a leading cause of morbidity and mortality.

Pulmonary embolism is a often complication of DVT and almost always occurs as a result of venous thrombosis.[2,3] Available data indicate that more than 90% of pulmonary emboli arise from thrombi in the venous system of the lower extremities.[4] The incidence of pulmonary embolism in conjunction with proven cases of DVT is 30% to 43%.[5]

Diagnosis of DVT based on clinical signs and symptoms alone is both non-specific and insensitive. DVT frequently are present in the absence of clinical signs and are absent in as many as 50% of patients in whom clinical signs and symptoms suggest their presence.[4] The clinical features of DVT arise from reactive inflammation, venous obstruction, and diversion of blood through the superficial veins. These features include pain, swelling, redness, warmth, tenderness, edema and prominent superficial veins.[6] None of these signs and symptoms are unique to DVT. In addition, various other disorders such as muscle strain, cellulitis or ruptured Baker's cyst can mimic the disease.[7] Clinical diagnosis is also complicated by non-obstructive thrombi with minimal symptoms such as those occurring post operatively.

Venous thromboembolism is a major cause of death and morbidity among hospitalized patients. The disease, however, is often clinically silent with pulmonary embolism going undetected in as many as 70% to 80% of the patients whose conditions are not diagnosed until autopsy. Therefore, it is suspected that the true incidence of venous thromboembolism may be significantly greater than actually quoted. This finding may be related to the relatively low rate of autopsies performed in non-acute care facilities such as rehabilitation hospitals and nursing homes where the incidence of pulmonary embolism may be higher.[10]

Although the signs and symptoms of DVT are absent in approximately 50% of the patients, they range from subtle to obvious in the remaining 50% of cases. The lack of objective clinical findings creates much difficulty in the diagnosis of DVT. At best, clinical examination alone indicates DVT in only 50% of cases, while falsely suggesting the diagnosis (false-positive results) in 30% to 60% of cases.[11] Once the clinician is alerted to the possibility of DVT, various diagnostic procedures may be carried out. Accurate diagnosis, however, is facilitated by an understanding and appreciation of the most common sites of thrombus formation, the likelihood of propagation, the type of patients at high risk, signs and symptoms, and proper testing.

ETIOLOGY

Risk factors associated with thrombus formation include trauma, especially following an operation or parturition, cardiac and vascular disorders, obesity, genetic predisposition, increasing age, an excess of erythrocytes or platelets, an overproduction of fibrinogen, and sepsis.

The three major recognized factors in the etiology of DVT are: local injury to vessels (injured endothelium), venous stasis or turbulence of blood flow, and alteration (hypercoagulability) of the blood itself.

Trauma

Injury to the endothelial surface of the vessel results in platelet and fibrin adherence to the subendothelial collagen. Release of adenosine diphosphate (ADP)

from damaged endothelial cells and red blood cells, and adherent platelets, augments the buildup of the platelet clump. This initial aggregation of platelets is reversible. However, irreversible aggregation quickly occurs due to thrombin formation through the activation of factor XII by exposed collagen (intrinsic pathway) and the release of thromboplastin from injured endothelium (extrinsic pathway).

Venous Stasis

Another leading cause of DVT is venous stasis. Venous stasis may be caused by factors such as prolonged immob-ilization, debilitating medical conditions, stroke, myocardial infarction, heart failure, obesity, varicose veins, anesthesia, and age greater than 65 years.

Hypercoagulopathy

Hypercoagulopathy also plays a role in the development of DVT. Hypercoagulation can be caused by a variety of factors including the following: hyperviscosity, increased platelet adhesiveness, malignant disease, high levels of estrogen, thrombocytosis, antiphospholipid syndrome, increased clotting factors, and increased levels of fibrinogen.[9]

THROMBUS EVENTS

A venous thrombus formation may be clinically asymptomatic, undergo spontaneous lysis, alter the venous circulation and cause symptoms. It also may propagate and possibly extend into the more proximal veins, embolize, or any combination of the aforementioned events may occur.

For example, in the situation of a thrombus in the acute formation process, it is highly likely that this thrombus (or a part thereof) will detach from the venous endothelium. This event can occur at any time during the formation process and may result in an embolus in the pulmonary system.

Chronic thrombus formations are usually incorporated into the wall of the veins. Long-term illnesses can result from possible venous valve damage and the development of postphlebitic syndromes.

PROPERTIES OF AN IDEAL DVT DETECTION PROCEDURE

The optimal approach in the detection of clinically suspicious DVT is the use of a diagnostic technique that is both sensitive and specific for all possible locations of thrombi in the deep veins of the legs. The technique should differentiate between acute and chronic thrombus, particularly since this is an important consideration in therapeutic decisions.[8] An ideal test should be readily available and convenient; provide a prompt, reliable result; and cause minimal discomfort to the patient. The test also should be cost effective and reproducible. A false-positive diagnosis can result in needless exposure to the risks of anti-coagulant therapy. A false-negative diagnosis may put the patient at risk of clot propagation, embolization and death.[2]

While there are many imaging procedures currently available to aid in the diagnosis of DVT, there is at present, no single test that meets all of the above criteria. Each of the modalities available has limitations. Therefore, the challenge is to find a single, non-invasive imaging method that will overcome the limitations of available tests and one that is capable of making a significant

contribution to the clinical and therapeutic management of this group of patients.

DETECTION TECHNIQUES

Contrast Venography

Contrast venography has been performed for more than 50 years[5] and was previously considered the technique of choice in the detection of DVT, due to its high sensitivity and specificity for the presence of clots in the lower extremities.[12] It is the only available method that provides information on all of the vessels in the venous system of the lower extremities, offering superior resolution when compared with other imaging modalities. Because the diagnosis of DVT is dependent on the detection of thrombi in these vascular areas, the diagnostic accuracy of contrast venography in this situation is high (96%). This method is, however, less accurate in the larger pelvic vessels because of contrast dilution.[5] It is important to note that while the complication rate associated with contrast administration may be reduced with the use of low-osmolar contrast media, venography is nevertheless an invasive procedure.[12] As such, it is often associated with contrast-induced side effects such as pain, allergic reactions, nausea, and vomiting.[13] Furthermore, contrast venography yields technically unsatisfactory findings in 10% to 15% of studies.[14] This modality also has limited feasibility in severely ill patients and cannot be performed in as many as 10% of patients such as those with poor venous access, a history of allergic reactions to contrast media, local infection of the leg, or renal insufficiency.[7]

Anatomical changes related to the presence of chronic thrombi can make a subsequent diagnosis of acute thrombosis difficult. At present, contrast venography is recommended only as an alternative procedure and its use should be limited to patients in whom there is a high clinical suspicion of DVT, or in cases in which ultrasound is unavailable or may be technically inadequate.[14]

Impedance Plethysmography

Impedance plethysmography (IPG) is a non-invasive procedure that takes advantage of the normal physiologic phenomenon of the venous volume change in the legs that occurs during respiration. In the presence of thrombi, the venous volume decreases correspondingly. IPG can detect thrombi that produce obstruction in the thigh, but it is unable to detect most thrombi in the calf. Furthermore, it is unable to differentiate between DVT and non-thrombotic causes of venous outflow obstruction. Tensing of the muscles, the presence of extravascular masses, or elevated venous pressure due to the presence of congestive heart failure can lead to false-positive results. The presence of diminished afferent arterial flow to the limbs in patients with peripheral arterial diseases also results in diminished efferent venous flow and can reduce the specificity of the test.[7,14]

Ultrasound

Compression ultrasound (CUS), which works on the principle of the failure of the vein to collapse under gentle external pressure, is regarded as the non-invasive technique of choice for detecting DVT in symptomatic patients.[15] CUS is preferred for initial investigations

in the diagnosis of acute DVT[8] above the knee and is more commonly used than IPG techniques in these cases.[16] CUS is a more comfortable procedure for the patient and it offers cost advantages when compared with contrast venography.[14] The reported sensitivity and specificity for common femoral vein DVT is in the range of 83% to 100%. Likewise, its sensitivity and specificity for DVT in the popliteal fossa is between 86% and 100%, respectively.[7] Results compiled from a number of investigations indicate an overall sensitivity of 95% and a specificity of 98% in the detection of DVT.[2] Although CUS is a quick and readily available diagnostic test, it is more difficult to perform in the veins of the calf because of the smaller size of the vessels, the slower blood flow and increased anatomical variance in the lower leg.[8] Its usefulness in patients with recurrent thrombosis is limited since changes from acute and chronic DVT may overlap.[17] Furthermore, CUS is not reliable in the management of asymptomatic post-operative patients who are at high risk for DVT.[15,18] This is possibly due to the small size of postoperative thrombi as well as the small amounts of venous and perivascular tissue inflammatory infiltrates in the early and occult stages of DVT.

Duplex ultrasonography uses real-time ultrasound techniques and is supplemented by Doppler flow, which allows the direct imaging of the venous circulation with simultaneous blood flow information. Studies using duplex ultrasound techniques for evaluation of proximal DVT reported high sensitivity and specificity, but its use in detection of thrombus below the knee is associated with much lower sensitivity due to poor visualization of the calf veins.[19]

The accuracy of ultrasound procedures employed in the detection of DVT is dependent on the training and experience of the operator.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) offers high sensitivity and specificity in the detection of DVT. MRI has demonstrated an advantage in the imaging of iliac and calf veins. While its high cost and limited availability discouraged its routine use in the diagnosis of DVT; it was later discovered that MRI is helpful in cases that require fine anatomical detail to provide decisive information relevant to patient management.[19] This form of technology presents the potential to further the availability of accurate diagnosis of DVT.[17]

NUCLEAR MEDICINE IMAGING TECHNIQUES

Many scintigraphic techniques currently in use or under investigation for use in the diagnosis of DVT have the possible advantage of distinguishing between acute, hematologically active thrombi and chronic thrombi, thus aiding in the selection of appropriate treatment. Hull and co-workers[20] have shown that objective diagnosis followed by selective anticoagulation therapy is significantly more cost-effective than treatment based solely on clinical grounds. A radiopharmaceutical agent that permits an accurate diagnosis of DVT would definitely decrease the morbidity and mortality associated with this condition since appropriate therapy could be offered accordingly. In economic terms, this would be manifested in savings for both the patient and hospital, since

hospital stays would be shorter. A definitive test should eliminate the need for additional diagnostic studies, thereby facilitating the delivery of appropriate treatment.

The development of any new radiopharmaceutical procedure for use in the diagnosis of DVT requires the consideration of a number of factors, including: availability and convenience, the time interval between injection and diagnostic result, and other issues such as rate of blood clearance, level of soft tissue background, specificity of agent for thrombi, as well as organ uptake.

Radionuclide Venography

The most commonly performed scintigraphic techniques for DVT to date are based on non-specific radionuclide venography. Radionuclide venography of the lower extremity performed with Tc-99m macroaggregated albumin can be used in conjunction with a perfusion lung scan. This technique produces images of the course of deep veins and collateral routes. It also may identify the clot itself. False-positive results can occur in areas of blood pooling, especially in regions of dilated, incompetent, or perforated veins.[21] Circulation within the deep veins also may be visualized with Tc-99m red-blood-cell venography.

The use of radionuclide venography is hindered by its poor resolution and its inability to identify the thrombus. Since it only identifies the site of occlusion, it is therefore unable to distinguish between extraluminal and intraluminal causes of thrombosis or distinguish active (or acute) thrombi from remitting (or chronic) thrombi. The results are variable distal to the popliteal veins and hence, the diagnosis of thrombi in the lower leg is not reliable.

In addition, this imaging technique can be labor intensive, requiring the efforts of as many as three staff members in order to carry out a study. The diagnostic accuracy of radionuclide venography is limited and it is rarely used clinically at present.[8] However, Tc-99m red-blood-cell venography may be considered when ultrasound and contrast venography procedures are technically difficult to perform. It may be of particular clinical value when the results are conclusive (e.g., definitely positive or negative).[17]

Platelet Scintigraphy

Platelet scintigraphy, which was initially introduced to diagnose DVT as well as directly monitor the efficacy of therapy, is a labor-intensive technique. It requires a radiolabeling procedure that takes at least two hours during which the platelets are separated from plasma and other cells. The technique requires as many as 48 hours to 72 hours for adequate platelet deposition and blood clearance. Both In-111 oxine and Tc-99m have disadvantages. In-111 oxine, commonly used for cell labeling, has the disadvantage of untoward radiation dosimetry, while the preferable Tc-99m has the disadvantage of a shorter half-life.

It is important to note that a significant drop in sensitivity and specificity for thrombi more than one day old, due to poor uptake characteristic of older thrombi, has been reported with the use of this imaging technique.[22] Thrombi must be fresh in order to be successfully imaged using radiolabeled platelets.[23] Anticoagulant therapy also may interfere with incorporation of labeled platelets into thrombi[24] potentially reducing this modality's sensitivity.

Fibrinogen Uptake and Fibrinogen Scintigraphy

The use of I-125 fibrinogen has been well documented as a useful screening agent for patients at high risk for developing DVT.[25,26] Since this agent is no longer available commercially, this non-imaging test is rarely used. A number of radiotracers with emissions useful for imaging have been investigated as radiolabels on fibrinogen. Fibrinogen, similar to radiolabeled platelets, is incorporated only onto freshly forming thrombi and is relatively insensitive to pre-existing thrombi.[27] Prompt diagnosis is hindered by prolonged blood circulation of fibrinogen and images are generally not diagnostic if obtained less than 24 hours post injection. Further exploration of labeled fibrinogen as an imaging agent has been limited due to concerns regarding its human origin because of the inherent risk of viral transmission as well as interference by anticoagulant drugs with incorporation of labeled fibrinogen into fresh thrombi.[22]

Immunoscintigraphy

Monoclonal Antibodies. Various monoclonal antibodies and their fragments which target platelets or fibrin are under clinical investigation for use in the diagnosis of DVT. Monoclonal antibodies have several advantages over other scintigraphic techniques by targeting essential components of thrombi with high specificity and affinity. Studies have shown that these proteins demonstrate lower absolute uptake to thrombi than radiolabeled fibrinogen. However, it is possible to obtain scintigraphic images sooner due to more rapid blood clearances of the protein. This makes it possible to investigate these potential agents using more advantageous radiolabels such as Tc-99m.

Both anti-platelet and anti-fibrin antibodies have been investigated.[22,23,28-33] Anti-fibrin antibodies show the greatest clinical utility in detecting active venous thrombosis.[29,34] Monoclonal antibodies directed against platelets may suffer from prolonged body background radioactivity and slow blood clearance as they also label circulating platelets. In this case, aged thrombi may not be visualized because of potentially inadequate deposits of new platelets. Monoclonal antibodies demonstrating high specificity for deposits of fibrin may have the advantage of localizing in mature thrombi, which contain high deposits of fibrin. Slow blood clearance has prevented early imaging with monoclonal antibodies. Delayed imaging is required several hours following injection in order to obtain diagnostic images even with smaller Fab and Fab′ fragments.[29,30] There is also concern regarding potential human anti-mouse antibody (HAMA) response.[35] The development of antibodies derived from human recombinant DNA technology could be of value in decreasing immunogenecity.[36]

Numerous antifibrin monoclonal antibodies directed against various antigenic receptors on the fibrin molecule are currently under investigation. An ideal radiolabeled monoclonal antibody would localize with high affinity to receptors on fibrin deposits of both fresh and aged thrombi with rapid and complete blood clearance of the circulating radiolabel.

Monoclonal antibodies that target antigens on the fibrin molecule include those reacting with the amino group on the alpha chain,[37] on the D domain of on-

cross-linked fibrin[29,38] and on cross-linked DD dimer regions.[29] The rationale for developing an antibody with high affinity for the DD domain of cross-linked fibrin is based on a unique epitope found only in cross-linked fibrin. This epitope is abundant throughout thrombi and readily accessible to blood-borne radiopharmaceuticals. It is not readily lost upon initial fibrin degradation, thus making older thrombi a potential target as well. There is the possibility that some of these monoclonal antibodies may have cross reactivity and may bind to cross-linked fibrin degradation products, but these proteins would not have reactions with fibrinogen. Cross-linked fibrin itself is the backbone of the formation of both venous and arterial thrombi and has numerous antigenic sites available compared with its parent fibrinogen molecule.[39]

The glycoprotein IIb/IIIa complex (GP IIb/IIIa) plays an integral role in thrombus formation by binding fibrinogen to facilitate platelet aggregation.[38] This GP IIb/IIIa receptor is expressed only on activated platelets. Therefore, proteins such as monoclonal antibodies that localize or bind to these receptors selectively bind to platelets intimately involved in the thromboembolic event making this an excellent target for the development of thrombus-imaging radiopharmaceutical agents.

Several monoclonal antibodies with activity at the GP IIb/IIIa receptor are being investigated as potential thrombus imaging agents. At the same time, there are other anti-platelet antibodies developed which target other receptor sites on activated platelets that are undergoing clinical trials to determine their potential as thrombus imaging agents.[22]

The advantage of antifibrin and antiplatelet monoclonal antibodies used in the detection of intravascular thrombi is their ability to recognize specific molecular sites exposed during various stages of thrombus formation and lysis. These antibodies can be digested enzymatically into fragments to enhance clearance from the blood pool and to promote more rapid excretion into the urine for prompt scintigraphic detection and diagnosis. Repeat imaging procedures with these proteins would be difficult due to the potential of HAMA responses, which increases significantly for any second administration.

Synthetic Peptides. A promising alternative to antibodies is the use of small peptides with similar affinities, namely those with platelet affinity.[40] These small peptides would be more advantageous than complex, high molecular weight antibodies or their fragments. Peptides can be produced synthetically which mimic the "backbone" sequences containing the active targeting portion of the protein, as well as a chelating agent for the attachment of radionuclides. These should be easier and less expensive to produce than more complex antibodies.[41] In addition, they are not antigenic and there is no danger of viral contamination. They also have more rapid blood clearance than antibodies.[22] These peptides can be synthesized to produce sequences similar to the active sites derived from monoclonal antibodies that have a high affinity for thrombi.

Earlier peptides have lower affinity for thrombi and rapid renal clearance resulting in low absolute accumulation.[40] However, smaller peptides, consisting of less than 20 amino acids, which contain a sequence of

arginine-glycine-aspartate (RGD), have been found to bind to the GP IIb/IIIa receptor. These smaller peptides were observed to effectively compete with endogenous fibrinogen for receptor binding sites.[42] In a study involving a small group of patients, a Tc-99m labeled peptide was shown to be useful in imaging peripheral venous thrombi within one to three hours post injection.[43] This agent which is designed to localize to the GP IIb/IIIa receptor on the surface of activated platelets is now available as a radiopharmaceutical kit for labeling with Tc-99m. This product Tc99m Apcitide, marketed as AcuTect™, is presently indicated for the detection and localization of acute venous thrombosis in the lower extremities. Another peptide, known presently as P748, which also has a high affinity for the GP IIb/IIIa receptor, has been shown to provide good image definition of femoral vein and lung thrombi in animals.[44] This agent is being investigated for its potential in the detection of pulmonary emboli.

Disintegrins

Disintegrins (also known as inhibitors of integrins) are small proteins that have been isolated from the venom of the American viper snake. These disintegrins bind to the GP IIb/IIIa receptor. It was discovered that these proteins have native RGD peptide sequences in a highly coiled manner containing multiple disulfide cross-linking bonds. Among a number of disintegrins investigated, iodine-123 radiolabeled bitistatin showed the best localizing characteristics in thrombus imaging with good absolute binding to thrombi and rapid blood pool clearance.[45, 46]

Recombinant Tissue Plasminogen Activator

Clinical studies performed with radiolabeled recombinant DNA tissue plasminogen activating factor (rt-PA) demonstrated reliable detection of proximal and distal vein thrombosis in both fresh and aged thrombi, and was unaffected by heparin therapy.[47] Tissue plasminogen activating factor, a naturally occurring serine protease enzyme with two functional sites that allows it to bind directly to fibrin and induce increases in plasminogen catalytic activity.[48] This fibrin-specific thrombolytic agent presents minimal adverse and immunogenic reactions typical of proteins derived using recombinant DNA techniques.

SUMMARY

A rational approach toward an objective diagnosis of DVT requires a method that is both sensitive and specific for all possible locations of thrombi, including the lower limb. There is obvious interest in the development of a reliable diagnostic test for this relatively common and life threatening clinical problem.

An ideal diagnostic modality should be readily available, relatively inexpensive, sensitive as well as specific for DVT, yield reproducible results, and be well tolerated by patients. Current clinical methods for diagnosing DVT are notoriously difficult or unreliable. Venography with contrast media is invasive and presents risks for patients with allergies, is associated with patient discomfort and may even possibly induce DVT. Ultrasound techniques, although generally accepted, have low rates of detection, particularly when imaging below the knee and is to a certain extent operator

dependent. Radiolabeled platelets are not useful in the diagnosis of older thrombi and complications may occur with the use of products of human origin, such as fibrinogen, which is derived from pooled plasma.

It seems that unique antigenic markers present only on components of thrombi may offer opportunities for the development of novel radiopharmaceuticals. The GP IIb/IIIa complex on activated platelets is one example of such a target.

Immunoscintigraphy techniques with monoclonal antibodies, or their fragments have shown promise as thrombus-imaging radiopharmaceuticals. However, these radiotracers may suffer from immunogenicity problems such as HAMA. The amino acids which comprise the biologically active portion of the monoclonal antibodies could be sequenced and replicated synthetically. These synthetic peptides, and those with native sequences that have a high affinity for thrombi, show promise in the detection of DVT.

Two independent strategies have been explored in the development of thrombi-localizing radiopharmaceuticals. The first is that agents selectively targeting platelets should have a higher affinity for arterial thrombi; and second, agents that preferentially localize in fibrin should exhibit stronger binding characteristics to older venous thrombi.[41] Regardless, all of these agents should localize in actively forming thrombi, thereby permitting scintigraphic imaging.

A clinically useful radiopharmaceutical capable of providing an accurate and timely diagnosis of DVT is needed to combat a common condition that affects a large population and is associated with significant morbidity and mortality.

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QUESTIONS

1. Thrombosis can be _____.
a. life threatening
b. life saving
c. both a and b
d. none of the above

2. Thrombosis refers to _____.
a. stroke
b. the formation of a clot
c. occlusion of an organ
d. hemorrhage

3. Mature thrombus formations would presently be better imaged with monoclonal antibodies raised against
a. fibrin
b. fibrinogen
c. platelets
d. subendothelial collagen

4. Synthetic peptides offer which of the following advantage(s) over monoclonal antibodies?
a. They are minimally antigenic with little danger of viral contamination
b. They have higher absolute affinities for thrombi
c. They localize in both platelets and fibrin in thrombi
d. All of the above

5. Pulmonary embolism usually occurs as a result of ____.

a. venous thrombosis
b. hemorrhage
c. sepsis
d. trauma

6. Data indicate that more than ___ percent of cases of pulmonary embolism arise from thrombi in the lower extremities.

a. 30
b. 50
c. 70
d. 90

7. All of the following are true **except**, synthetic peptides can be produced to have _____.

a. the active antigen binding sequences of a monoclonal antibody
b. a chelating agent or site to which a radiolabel can be attached
c. high molecular weights for better body clearance
d. platelet affinity

8. Which of the following is **not** a clinical feature of DVT?

a. pain
b. swelling
c. edema
d. vomiting

9. A false-negative diagnosis of DVT can result in all of the following **except** ____.

a. needless exposure to anticoagulant therapy
b. clot propagation
c. embolization
d. death

10. Which of the following is **not** a predisposing factor in thrombus formation?

a. underproduction of fibrinogen
b. sepsis
c. obesity
d. increasing age

11. Advantages of developing a monoclonal antibody in the detection of thrombi include the following, **except** __.

a. they can be targeted to specific molecular sites
b. they can be enzymatically reduced to their fragments to enhance clearance from circulation
c. they have the potential for HAMA responses
d. longer blood pool activity makes delayed imaging possible.

12. Fibrinogen has been well documented for use as a thrombus detection agent but it is not used clinically now because

a. it localizes only on freshly forming thrombi
b. it has a long blood circulation time
c. it is a product of human origin
d. is no longer commercially available

13. The GP IIb/IIIa complex is a potential receptor for developing thrombus localizing radiopharmaceuticals because it is present only on _____.

a. fibrin on the thrombus
b. platelets in the blood
c. fibrinogen
d. activated platelets

14. Radiolabeled platelet scintigraphy is useful in thrombus imaging as ____.

a. it is a quick and simple process to label the cells
b. it localizes in both fresh and mature thrombi
c. the sensitivity of the test is not affected by anticoagulants
d. diagnosis can be obtained within 24 hours of the test

15. The use of clinical examination alone may give a false-positive diagnosis of DVT in ___ of patients.

a. 10% to 40%
b. 20% to 50%
c. 30% to 60%
d. 40% to 70%

16. ___ is the only available imaging method that provides information about all of the vessels in the venous system of the lower extremity.

a. contrast venography
b. impedance plethysmography
c. compression ultrasound
d. none the above

17. An advantage of radionuclide venography is its ____.

a. superb resolution
b. consistent results
c. reduced labor requirements
d. none of the above

18. When imaging DVT, for which of the following techniques is there a concern due to a significant drop in sensitivity and specificity for thrombi greater than one day old?

a. platelet scintigraphy
b. impedance plethysmography
c. compression ultrasound
d. magnetic resonance imaging

19. Which of the following offers several advantages over other imaging techniques by offering targeting with high specificity for platelets or fibrin?

a. contrast venography
b. platelet scintigraphy
c. fibrinogen scintigraphy
d. immunoscintigraphy

20. Which of the following has the greatest clinical utility in detecting active venous thrombosis?

a. anti-platelet antibodies
b. anti-fibrin antibodies
c. human anti-mouse antibodies
d. none of the above

21. ____ are small proteins isolated from the venom of the viper snake.

a. integrins
b. disintegrins
c. glycoproteins
d. early peptides

22. Which of the following is preferred for initial investigations in the diagnosis of acute DVT above the knee?

a. contrast venography
b. radionuclide venography
c. compression ultrasound
d. IPG

23. Which is the most common site for thrombosis?

a. the lungs
b. the heart
c. the brain
d. the lower extremities

24. Which of the following disorders can mimic DVT?

a. ruptured Baker's cyst
b. muscle strain
c. cellulitis
d. all of the above

25. All of the following are predisposing factors associated with thrombus formation except one. Select the inappropriate factor.

a. excess of erythrocytes
b. over production of fibrinogen
c. cardiac and vascular disorders
d. cholecystitis