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Diagnosis of DVTs and PE's - New Imaging tools & modalities

Farbod N. Rahaghi, M.D., Ph.D.,

Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School.
15 Francis Street, Boston MA 02115, frahaghi@bwh.harvard.edu; Phone: 617-632-6770

Jasleen K. Minhas, M.D., and

Department of Medicine, North Shore Medical Center, jminhas@partners.org 81 highland Ave
Salem MA 10970, Phone: 978-354-4801

Gustavo A. Heresi, M.D., M.S.

Respiratory Institute, heresig@ccf.org Cleveland Clinic, Mail code A90, 9500 Euclid Ave, OH
44195, Phone: 216-636-5327

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Introduction

Untreated venous thromboembolism (VTE) carries a potential for serious complications and mortality. At the same time, there is also significant risk associated with treatment with anticoagulation and thrombolysis. This leads to a need for sensitivity in diagnosis, certainty in the decision not to treat, as well as relative urgency in making the diagnosis and initiation of treatment. Thus, there is significant impetus to develop and refine tools for detection and management of venous thrombosis, both in the extremities and the lungs. While the importance of these clinical decisions necessitates a comprehensive clinical approach to diagnosis, imaging has long played a pivotal role in detecting the presence and extent of thromboembolic disease. While many great imaging tools already exist, furthering the application of imaging in thromboembolism remains an area of intense research and development.

Within the realm of imaging, there has been a steady progression towards using non-invasive methods to guide initial diagnosis, with invasive imaging used in complex cases or as part of an interventional strategy. Research has historically focused on the question of detection of clot which then inputs into the clinical decision making pathways. However, as the number

Correspondence to: Farbod N. Rahaghi.

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of tools and options for treatment increase, there is growing interest in using imaging for better quantification and classification of thromboembolic disease to improve prognostication and to guide intervention.

In this section, we review the role of imaging in the diagnosis and management of deep venous thrombosis (DVT) and pulmonary embolism (PE), highlighting the current state of the art modalities as well as areas in which current research is uncovering promising tools that may find their way to clinical use in the near future.

Imaging in the Detection and Management of DVT

Contrast venography is an invasive procedure in which venous opacification is evaluated in real time. Although the gold standard for detection of DVT, this method is rarely practiced outside of expert centers where it is often used in the context of intervention.^{1,2} This is in large part due to the myriad of non-invasive imaging techniques which are now widely available, and in particular, the use of ultrasound in the diagnosis of DVT.

Methods using ultrasound to evaluate VTE were developed in the 1960s³ and were perfected in the following decades. The measurement of venous blood flow as well as venous compressibility^{4,5} were also developed. The evaluation of venous compressibility in combination with color and spectral Doppler assessment of flow and phase is now the recommended approach for detection of venous clot^{2,6} (Figure 1). This is largely due to the availability and ease of deployment in a variety of clinical settings.⁶ While the incidence of upper extremity DVT is much lower than the lower extremity, its presence leads to a significant risk of PE and associated morbidity.^{7,8} Imaging approaches similar to the lower extremity can be used for the detection of clot in the upper extremities. However, restrictions imposed by the clavicle significantly limit ultrasound based techniques.^{2,9}

Other imaging modalities have been investigated for clot detection and have shown promising results, though none have replaced ultrasound based methods in routine clinical settings. As an analogue of direct venography, CT based venography (involving direct injection of contrast into the veins) has been shown to have great sensitivity in detection of DVT¹⁰ while reducing contrast load by as much as 80% compared to conventional venography. Additionally, venography using contrast injected in a distal site, for example in the context of a CT angiography of the chest, have also been investigated.¹¹ This approach is proposed given the common risk factors between PE and DVT as well as the observation that many individuals with no evidence of PE on CT angiography are noted to have DVT.¹¹ This approach to CT angiography also improves the ability to detect proximal clot in the pelvis.¹² Subsequent studies of this combined approaches have shown limited utility with additional radiation with both angiography and venography (but not contrast) exposure. Thus, despite initial promising results, this combined use as a routine approach remains controversial.^{13,14}

Many promising studies have been performed to assess the utility of MRI venography as a tool for detection of DVT. Those with contrast have had a good sensitivity but carry risks associated with contrast loads.^{15,16} Noncontrast studies have limited the ability to visualize

subacute and chronic clot.¹⁷ Meta-analyses of these studies^{18,19} have not yielded sufficient evidence for replacement of ultrasound approaches by MRI as standard of care.

While the dominance of ultrasound based techniques has made this the most commonly used tool for detection of DVT, alternative imaging modalities have an evolving role in clot detection in cases where ultrasound has limitations as well as for defining the chronicity and composition of clot. While ultrasound is widely available, patient body habitus can provide a significant limitation in use of ultrasound techniques.^{2,19} Additionally, ultrasound based techniques are not reliable in cases of suspected proximal DVT.²⁰ In these cases, Magnetic Resonance Venography as well as CT approaches can provide an alternative mean to diagnose and define the extent of thrombus.

Determination of the age of thrombus is clinically relevant in order to determine cause and to establish efficacy of treatment. Ultrasound abnormalities can persist in 50% of patients a year out from initial diagnosis of DVT²¹ leading to a diagnostic dilemma of identifying recurrent clot particularly in the same anatomic location in at risk patients.²² MRI offers the opportunity to differentiate between old and new thrombi,²² leveraging the ability of MRI to differentiate between age of thrombi. Modifications including “Black-Blood Thrombus Imaging (BTI)”^{23,24} have shown promise in dating clot chronicity. Sonographic elasticity imaging (SEI) utilizes ultrasound based techniques to assess the stiffness of clot and thus distinguish fresh from subacute/chronic clot.^{25,26} Photo acoustic imaging, combined with ultrasound may also be helpful with defining the extent and age of clot.²⁷ Molecular imaging, which involves using specific targeted molecules to enhance and detect thrombus, has led to a number of proposed approaches to examine clot chronicity.²⁸ As an example, (99m)Tc-recombinant tissue plasminogen activator (rt-PA) has been used to determine the age of clot given the differential activity of rt-PA in old versus new thrombus.²⁹ Similarly, F-FDG-PET scanning has shown that FDG activity of clot decreases with time and thus can be used in assessing the age of clots of size detectable by F-FDG.³⁰ Methods of fluorescence based molecular imaging have also been developed to quantify fibrin deposition.³¹ Differentiating between bland and tumor thrombus is also a clinically important question because of the fundamentally different approach to treatment. In this context, PET imaging for classification based on the activity of the thrombus has shown promise for assessing clot tumor burden.^{28,32-35}

Pulmonary Embolus

Untreated pulmonary embolism (PE) can have potentially fatal consequences. The clinical diagnosis of PE currently relies on a framework where the clinical suspicion of the presence of clot is altered by tests, usually imaging, leading to final clinical diagnosis. This process also yields further prognostic information, including degree of right ventricular strain and clot burden which in addition to the patient’s hemodynamic status guides further intervention. . Selective pulmonary angiography, the gold standard for detection of pulmonary emboli, has largely been replaced by CT angiography and nuclear ventilation-perfusion scans (V/Q Scans) embedded within this clinical decision-making flow (Figure 2).

Despite this, limitations exist in detection of clot using imaging alone. In the case of CT angiography, there remains uncertainty around findings of isolated sub-segmental PE.³⁶ Additionally, there is significant concern about contrast induced nephropathy.³⁷ In the case of the V/Q scan, the degradation of the clinical utility of the test in the context of pre-existing or co-evolving lung disease presents a significant limitation.³⁸ This is further complicated by the significant presence of renal disease for CT angiography and lung disease for V/Q scans in the most at-risk populations for PE. Thus, in addition to improving these techniques, there remains significant interest in developing additional modalities for detection of clot.

Diagnostic Algorithm and the Use of Imaging Modalities

In patients with symptoms concerning for PE, use of probability criteria such as Wells or Geneva Score is the initial step in determining likelihood of disease. Application of both traditional and modified versions of these scores has been validated and is well-established.³⁹ Pulmonary Embolism Rule-out Criteria (PERC) can be subsequently utilized in individuals with a low risk. Further workup may be deferred in those with a negative PERC.³⁹ (Appendix 1)

A low risk probability criteria with a positive PERC warrants further testing with a D-dimer. Enzyme linked immunosorbent assay (ELISA) based D-dimer assays have a sensitivity of greater than 95%. D-dimer levels normally increase with age and adjusting the upper limit of normal (age multiplied by 10 in patients 50 years or older) for interpretation improves the sensitivity and specificity in this population.³⁹ A negative D-dimer combined with low probability criteria on Wells or Geneva criteria negates the need for further testing.³⁹

A moderate / high risk on probability criteria or positive D - dimer assay warrants further workup for PE. CT angiography (Figure 4) continues to be the mainstay for diagnosis of acute PE due to its high specificity. Combination of CT angiography with clinical probability criteria further increases predictive values as demonstrated by the PIOPED II study.⁴⁰⁻⁴² Thus, a negative CT in a non-high-risk patient is adequate to rule out PE. Additionally, once a diagnosis of PE has been established, the CT finding of increased RV:LV ratio may further aid in risk stratification and management.⁴³⁻⁴⁵

A V/Q scan may be of use in patients with a high risk on probability criteria but potentially falsely negative CT angiography. It may also be a preferential initial diagnostic study in conditions where CT angiography is contraindicated such renal failure or contrast allergy.⁴³⁻⁴⁵

CT Angiography for Diagnosis and Prognostication

CT angiography has largely replaced the use of pulmonary angiography and nuclear studies in the detection of PE. While initially the low resolution of CT scanning led to concerns about poor detection of smaller embolus,⁴⁶ the advent of multi-detector CT scanning (MDCT) leading to higher resolution has improved detection of smaller clot.⁴⁷ The PIOPED II study has been largely used to define the role of CT angiography in the context of decision making algorithm.⁴⁸ The study showed high specificity of CT angiography for detection of

PE (96%) but also raised concerns about sensitivity (83%) particularly for the detection of small subsegmental PE.³⁶ It also noted the limited sensitivity of CT angiography in the context of high clinical suspicion and recommended further investigations if CT angiography was negative in this population. It is important to note that many of the centers in PIONEER II used 4 slice MDCT and currently 64 slice MDCT are becoming increasingly common with 256 and 512 slice MDCT becoming now also available.⁴⁹ Thus, further studies are needed to clarify the impact of improving scanner technology on detection of small PE.

The risk of contrast-induced nephropathy has been a major barrier to use of CT angiography as many patients at risk for PE either have chronic kidney disease or are suffering from acute kidney injury in the context of hemodynamic compromise.^{37,50-52} While it is generally believed that this risk is significant, it has not been well quantified and recent studies suggest that it may be overestimated.⁵³⁻⁵⁵ These discrepancies arise from lack of randomized controls, differing definitions of clinically relevant AKI, and fluctuations in creatinine in such populations,⁵⁶ as well as changes in the nature and dosing of contrast currently administered as compared to the initial studies.⁵³

CT angiography has also been explored as a means for prognostication. Recently, prognostication models have been developed leveraging CT imaging to detect evidence of right ventricular strain. While most CT angiograms are non-ECG gated, which leads to an imprecise size estimation of the ventricles, initial studies suggest that cardiac size obtained from non-ECG gated scans still contain prognostic information.⁵⁷ The most commonly studied and validated marker has been the ratio of the diameter of the right ventricle to the left ventricle, which is used to detect “RV Strain” as a precursor to impending RV failure. This measure has shown validity in predicting progression to RV failure⁴³⁻⁴⁵ in particular when combined with other clinical information.⁵⁸ The detection and calculation of this ratio has recently been automated requiring no human operator input⁵⁹ and is becoming increasingly part of the prognostic information used for triaging patients with potential for deterioration, though its lack of specificity requires additional studies such as echocardiography for critical decision making.⁶⁰

Subjective and objective quantification of the location and burden of clot has also been explored.⁶¹ The location and extent of clot is known to be associated with evidence of heart dysfunction.^{62,63} Quantity of clot can be integrated into models to predict right ventricular dysfunction,⁶⁴ including those assessing maximal clot size.⁶⁵ While these methods are promising, further studies to build consensus on the best method of measuring clot burden are ongoing.

Assessing Regional Perfusion Using Nuclear Imaging

Evaluation of lung perfusion defects using nuclear imaging, combined with concurrent imaging of ventilation defects continues to be one of the key approaches to evaluation of PE.⁶⁶ The PIONEER I study established the utility of the V/Q scan in detection of PE, and in particular the diagnostic value of a normal V/Q study.^{67,68} Significant research has led to improvement of interpretation of V/Q scans and the data from PIONEER I study and the

subsequent PIOPED II study have led to the modifications of PIOPED II guidelines for image interpretation.⁴⁰⁻⁴²

SPECT (Single Photon Emission Computed Tomography) imaging uses tomographic techniques to create 3D reconstructions like Computed Tomography, but instead uses gamma rays emitted from injected tracers. Unlike traditional V/Q scans which are based on multiple planes, this method creates true 3D images. The use of 3D reconstruction information has been shown to improve diagnostic accuracy over planar reconstructions⁶⁹⁻⁷¹ particularly when used in conjunction with CT (CT-SPECT).⁷² However, large multicenter studies are currently lacking to define the role of SPECT and CT-SPECT in detection of PE.^{73,74}

The role of MRI in PE

Non-contrast enhanced and contrast enhanced MRI techniques have been leveraged for many years in detecting PE^{75,76,77} with similar findings to CT scans including luminal filling defects and vascular “cut-off” (Figure 5). However, the nature of numerous tissue air transitions and significant artifacts limit the use of traditional MRI in detection of small pulmonary emboli,⁷⁸ leading to concerns about sensitivity in detection.^{79,80} The utility of Gadolinium enhanced MRI in clot detection was evaluated systematically in the PIOPED III study which demonstrated great specificity (99%) but low sensitivity (78%) and further highlighted the variations between centers in terms of the adequacy imaging acquired.⁸¹

Thus, use of traditional MRI techniques as a general initial approach for detection of PE is not currently recommended.^{82,83} However, single center experiences appear promising that with appropriate tools, training and program-focused approach, MRI can be used for this purpose.⁸⁴

In an effort to improve clot detection using MRI, research has focused on use of molecular markers targeted towards fibrin,^{85,86} alpha2-antiplasmin^{87,88} and platelets.⁷⁸ Additionally, stepwise protocols have been proposed and assessed that take advantage of the variety of MRI protocols available to improve the speed and accuracy of clot detection using MRI.⁸⁹

In addition to the detection of PE, MRI is also being considered for novel uses such as non-invasive estimation of pulmonary vascular resistance⁹⁰ as well as development of perfusion mapping similar in concept to those obtained using nuclear studies.

Dual Energy Computed Tomography

The response of materials being penetrated by x-ray is used in CT to generate 3D representation of material density, which is the basis for CT imaging. However, when two x-rays of differing energy are present, the differential response to each energy provides the ability to infer material composition in addition to density. While this potential has been known since the 1970s,⁹¹ the technologic limitation of simultaneously emitting and detecting two different x-ray energies while not exposing the patient to double the dose of radiation limited the clinical deployment of this technology. Multiple solutions to this technical challenge have been developed and tested resulting in Dual Energy CT scans becoming clinically available in many centers. In the current implementations, the radiation

dosage, use of contrast and the patient/provider experience are not significantly different, and thus these scanners can be incorporated into routine clinical care without significant retooling of the work-flow.

One common use of DECT is to create quantifiable perfusion maps based on density of iodine outside of the vasculature, which provide a more robust 3D representation of penetration of iodine into the distal tissue (figure 6).⁹² This is then used to detect perfusion defects in a similar manner to MRI and SPECT approaches⁹³ with comparable results.⁹⁴ Multiple studies have evaluated the utility of DECT in improving the diagnosis of PE.⁹⁵ Blood volume detected using this approach has also been shown to be related to right heart strain in patients with PE⁹³ and improve the detection of pulmonary embolus, particularly in the peripheral lung.^{96,97} DECT has also shown significant promise in the study of Chronic thromboembolic pulmonary hypertension³⁹⁹⁸ as well as in distinguishing tumor embolism from thromboembolism.⁹⁹

Conclusion

In conclusion, imaging continues to play a pivotal role in the diagnosis of venous thromboembolism. Advances in imaging technology continues to improve the diagnostic utility of imaging and increasing experience with imaging has allowed it to become integrated into clinical decision making tools. Development of new technology and processing algorithms continue to expand the role of imaging in both prognostication and subtyping of disease which is likely to improve the utility of imaging in clinical treatment of venous thromboembolism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. de Valois JC, van Schaik CC, Verzijlbergen F, van Ramshorst B, Eikelboom BC, Meuwissen OJ. Contrast venography: from gold standard to 'golden backup' in clinically suspected deep vein thrombosis. *Eur J Radiol.* 1990;11(2):131–137. [PubMed: 2253634]
2. Karande GY, Hedgire SS, Sanchez Y, et al. Advanced imaging in acute and chronic deep vein thrombosis. *Cardiovasc Diagn Ther.* 2016;6(6):493–507. [PubMed: 28123971]
3. Sigel B, Popky GL, Wagner DK, Boland JP, Mapp EM, Feigl P. Comparison of clinical and Doppler ultrasound evaluation of confirmed lower extremity venous disease. *Surgery.* 1968;64(1):332–338. [PubMed: 5658736]
4. Cronan JJ. History of venous ultrasound. *J Ultrasound Med.* 2003;22(11):1143–1146. [PubMed: 14620883]
5. Raghavendra BN, Horii SC, Hilton S, Subramanyam BR, Rosen RJ, Lam S. Deep venous thrombosis: detection by probe compression of veins. *J Ultrasound Med.* 1986;5(2):89–95. [PubMed: 3514943]

6. Tapson VF, Carroll BA, Davidson BL, et al. The diagnostic approach to acute venous thromboembolism. Clinical practice guideline. American Thoracic Society. *Am J Respir Crit Care Med*. 1999;160(3):1043–1066. [PubMed: 10471639]
7. Munoz FJ, Mismetti P, Poggio R, et al. Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE Registry. *Chest*. 2008;133(1):143–148. [PubMed: 17925416]
8. Kooij JD, van der Zant FM, van Beek EJ, Reekers JA. Pulmonary embolism in deep venous thrombosis of the upper extremity: more often in catheter-related thrombosis. *Neth J Med*. 1997;50(6):238–242. [PubMed: 9232088]
9. Chin EE, Zimmerman PT, Grant EG. Sonographic evaluation of upper extremity deep venous thrombosis. *J Ultrasound Med*. 2005;24(6):829–838; quiz 839–840. [PubMed: 15914687]
10. Baldt MM, Zontsich T, Stumppfen A, et al. Deep venous thrombosis of the lower extremity: efficacy of spiral CT venography compared with conventional venography in diagnosis. *Radiology*. 1996;200(2):423–428. [PubMed: 8685336]
11. Cham MD, Yankelevitz DF, Shaham D, et al. Deep venous thrombosis: detection by using indirect CT venography. The Pulmonary Angiography-Indirect CT Venography Cooperative Group. *Radiology*. 2000;216(3):744–751. [PubMed: 10966705]
12. Loud PA, Katz DS, Bruce DA, Klippenstein DL, Grossman ZD. Deep venous thrombosis with suspected pulmonary embolism: detection with combined CT venography and pulmonary angiography. *Radiology*. 2001;219(2):498–502. [PubMed: 11323478]
13. Goodman LR, Sostman HD, Stein PD, Woodard PK. CT venography: a necessary adjunct to CT pulmonary angiography or a waste of time, money, and radiation? *Radiology*. 2009;250(2):327–330. [PubMed: 19188309]
14. Reichert M, Henzler T, Krissak R, et al. Venous thromboembolism: additional diagnostic value and radiation dose of pelvic CT venography in patients with suspected pulmonary embolism. *Eur J Radiol*. 2011;80(1):50–53. [PubMed: 21497470]
15. Moody AR. Magnetic resonance direct thrombus imaging. *J Thromb Haemost*. 2003;1(7):1403–1409. [PubMed: 12871274]
16. Arnoldussen C, Strijkers R, Lambregts D, Lahaye M, de Graaf R, Wittens C. Feasibility of identifying deep vein thrombosis characteristics with contrast enhanced MR-Venography. *Phlebology*. 2014;29(1 suppl):119–124. [PubMed: 24843097]
17. Westerbeek RE, Van Rooden CJ, Tan M, et al. Magnetic resonance direct thrombus imaging of the evolution of acute deep vein thrombosis of the leg. *J Thromb Haemost*. 2008;6(7):1087–1092. [PubMed: 18433464]
18. Sampson FC, Goodacre SW, Thomas SM, van Beek EJ. The accuracy of MRI in diagnosis of suspected deep vein thrombosis: systematic review and meta-analysis. *Eur Radiol*. 2007;17(1):175–181. [PubMed: 16628439]
19. Abdalla G, Fawzi Matuk R, Venugopal V, et al. The diagnostic accuracy of magnetic resonance venography in the detection of deep venous thrombosis: a systematic review and meta-analysis. *Clin Radiol*. 2015;70(8):858–871. [PubMed: 26091753]
20. Davidson BL, Elliott CG, Lensing AW. Low accuracy of color Doppler ultrasound in the detection of proximal leg vein thrombosis in asymptomatic high-risk patients. The RD Heparin Arthroplasty Group. *Ann Intern Med*. 1992;117(9):735–738. [PubMed: 1416575]
21. Piovela F, Crippa L, Barone M, et al. Normalization rates of compression ultrasonography in patients with a first episode of deep vein thrombosis of the lower limbs: association with recurrence and new thrombosis. *Haematologica*. 2002;87(5):515–522. [PubMed: 12010666]
22. Huisman MV, Klok FA. Current challenges in diagnostic imaging of venous thromboembolism. *Hematology Am Soc Hematol Educ Program*. 2015;2015:202–209. [PubMed: 26637722]
23. Xie G, Chen H, He X, et al. Black-blood thrombus imaging (BTI): a contrast-free cardiovascular magnetic resonance approach for the diagnosis of non-acute deep vein thrombosis. *J Cardiovasc Magn Reson*. 2017;19(1):4. [PubMed: 28095878]
24. Treitl KM, Treitl M, Kooijman-Kurfuerst H, et al. Three-dimensional black-blood T1-weighted turbo spin-echo techniques for the diagnosis of deep vein thrombosis in comparison with contrast-enhanced magnetic resonance imaging: a pilot study. *Invest Radiol*. 2015;50(6):401–408. [PubMed: 25783228]

25. Lubinski MA, Emelianov SY, O'Donnell M. Speckle tracking methods for ultrasonic elasticity imaging using short-time correlation. *IEEE Trans Ultrason Ferroelectr Freq Control*. 1999;46(1): 82–96. [PubMed: 18238401]
26. Rubin JM, Xie H, Kim K, et al. Sonographic elasticity imaging of acute and chronic deep venous thrombosis in humans. *J Ultrasound Med*. 2006;25(9):1179–1186. [PubMed: 16929019]
27. Karpouk AB, Aglyamov SR, Mallidi S, et al. Combined ultrasound and photoacoustic imaging to detect and stage deep vein thrombosis: phantom and ex vivo studies. *J Biomed Opt*. 2008;13(5): 054061. [PubMed: 19021440]
28. Houshmand S, Salavati A, Hess S, Ravina M, Alavi A. The role of molecular imaging in diagnosis of deep vein thrombosis. *Am J Nucl Med Mol Imaging*. 2014;4(5):406–425. [PubMed: 25143860]
29. Brighton T, Janssen J, Butler SP. Aging of acute deep vein thrombosis measured by radiolabeled 99mTc-rt-PA. *J Nucl Med*. 2007;48(6):873–878. [PubMed: 17504873]
30. Rondina MT, Lam UT, Pendleton RC, et al. (18)F-FDG PET in the evaluation of acuity of deep vein thrombosis. *Clin Nucl Med*. 2012;37(12):1139–1145. [PubMed: 23154470]
31. Hara T, Bhayana B, Thompson B, et al. Molecular imaging of fibrin deposition in deep vein thrombosis using fibrin-targeted near-infrared fluorescence. *JACC Cardiovasc Imaging*. 2012;5(6): 607–615. [PubMed: 22698530]
32. Sharma P, Kumar R, Jeph S, et al. 18F-FDG PET-CT in the diagnosis of tumor thrombus: can it be differentiated from benign thrombus? *Nucl Med Commun*. 2011;32(9):782–788. [PubMed: 21799368]
33. Sharma P, Kumar R, Singh H, et al. Imaging thrombus in cancer patients with FDG PET-CT. *Jpn J Radiol*. 2012;30(2):95–104. [PubMed: 22205138]
34. Erhamamci S, Reyhan M, Nursal GN, Torun N, Yapar AF. Incidental diagnosis of tumor thrombosis on FDG PET/CT imaging. *Rev Esp Med Nucl Imagen Mol*. 2015;34(5):287–294. [PubMed: 26025479]
35. Davidson T, Goitein O, Avigdor A, Zwas ST, Goshen E. 18F- FDG-PET/CT for the diagnosis of tumor thrombosis. *Isr Med Assoc J*. 2009;11(2):69–73. [PubMed: 19432032]
36. Carrier M, Righini M, Wells PS, et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. *J Thromb Haemost*. 2010;8(8):1716–1722. [PubMed: 20546118]
37. Kooiman J, Klok FA, Mos IC, et al. Incidence and predictors of contrast-induced nephropathy following CT-angiography for clinically suspected acute pulmonary embolism. *J Thromb Haemost*. 2010;8(2):409–411. [PubMed: 19943871]
38. Hayes SA, Soff GA, Zabor EC, Moskowitz CS, Liu CC, Ginsberg MS. Clinical consequences of an indeterminate CT pulmonary angiogram in cancer patients. *Clin Imaging*. 2014;38(5):637–640. [PubMed: 24928823]
39. Hoey ET, Mirsadraee S, Pepke-Zaba J, Jenkins DP, Gopalan D, Screaton NJ. Dual-energy CT angiography for assessment of regional pulmonary perfusion in patients with chronic thromboembolic pulmonary hypertension: initial experience. *AJR Am J Roentgenol*. 2011;196(3): 524–532. [PubMed: 21343493]
40. Yazdani M, Lau CT, Lempel JK, et al. Historical Evolution of Imaging Techniques for the Evaluation of Pulmonary Embolism. *Radiographics*. 2015;35(4):1245–1262. [PubMed: 26172362]
41. Sostman HD, Miniati M, Gottschalk A, Matta F, Stein PD, Pistolesi M. Sensitivity and specificity of perfusion scintigraphy combined with chest radiography for acute pulmonary embolism in PIOPED II. *J Nucl Med*. 2008;49(11):1741–1748. [PubMed: 18927339]
42. Sostman HD, Stein PD, Gottschalk A, Matta F, Hull R, Goodman L. Acute pulmonary embolism: sensitivity and specificity of ventilation-perfusion scintigraphy in PIOPED II study. *Radiology*. 2008;246(3):941–946. [PubMed: 18195380]
43. Lu MT, Cai T, Ersoy H, et al. Interval increase in right-left ventricular diameter ratios at CT as a predictor of 30-day mortality after acute pulmonary embolism: initial experience. *Radiology*. 2008;246(1):281–287. [PubMed: 18096540]
44. Kumamaru KK, Hunsaker AR, Wake N, et al. The variability in prognostic values of right ventricular-to-left ventricular diameter ratios derived from different measurement methods on

computed tomography pulmonary angiography: a patient outcome study. *J Thorac Imaging*. 2012;27(5):331–336. [PubMed: 22139353]

45. Jia D, Zhou XM, Hou G. Estimation of right ventricular dysfunction by computed tomography pulmonary angiography: a valuable adjunct for evaluating the severity of acute pulmonary embolism. *J Thromb Thrombolysis*. 2017;43(2):271–278. [PubMed: 27734186]
46. Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review. *Ann Intern Med*. 2000;132(3):227–232. [PubMed: 10651604]
47. Goodman LR. Small pulmonary emboli: what do we know? *Radiology*. 2005;234(3):654–658. [PubMed: 15734923]
48. Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med*. 2006;354(22):2317–2327. [PubMed: 16738268]
49. Douma RA, Hofstee HM, Schaefer-Prokop C, et al. Comparison of 4- and 64-slice CT scanning in the diagnosis of pulmonary embolism. *Thromb Haemost*. 2010;103(1):242–246. [PubMed: 20062931]
50. Schrader R. Contrast material-induced renal failure: an overview. *J Interv Cardiol*. 2005;18(6):417–423. [PubMed: 16336421]
51. Mitchell AM, Kline JA, Jones AE, Tumlin JA. Major Adverse Events One Year After Acute Kidney Injury After Contrast-Enhanced Computed Tomography. *Ann Emerg Med*. 2015;66(3):267–274 e264. [PubMed: 26004770]
52. Mitchell AM, Jones AE, Tumlin JA, Kline JA. Incidence of contrast-induced nephropathy after contrast-enhanced computed tomography in the outpatient setting. *Clin J Am Soc Nephrol*. 2010;5(1):4–9. [PubMed: 19965528]
53. Hinson JS, Ehmann MR, Fine DM, et al. Risk of Acute Kidney Injury After Intravenous Contrast Media Administration. *Ann Emerg Med*. 2017;69(5):577–586 e574. [PubMed: 28131489]
54. McDonald RJ, McDonald JS, Bida JP, et al. Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? *Radiology*. 2013;267(1):106–118. [PubMed: 23360742]
55. McDonald JS, McDonald RJ, Carter RE, Katzberg RW, Kallmes DF, Williamson EE. Risk of intravenous contrast material-mediated acute kidney injury: a propensity score-matched study stratified by baseline-estimated glomerular filtration rate. *Radiology*. 2014;271(1):65–73. [PubMed: 24475854]
56. Sinert R, Brandler E, Subramanian RA, Miller AC. Does the current definition of contrast-induced acute kidney injury reflect a true clinical entity? *Acad Emerg Med*. 2012;19(11):1261–1267. [PubMed: 23167857]
57. Gutte H, Mortensen J, Mork ML, et al. Non-ECG-gated CT pulmonary angiography and the prediction of right ventricular dysfunction in patients suspected of pulmonary embolism. *Clin Physiol Funct Imaging*. 2016.
58. Kumamaru KK, George E, Ghosh N, et al. Normal ventricular diameter ratio on CT provides adequate assessment for critical right ventricular strain among patients with acute pulmonary embolism. *Int J Cardiovasc Imaging*. 2016;32(7):1153–1161. [PubMed: 27076224]
59. Kumamaru KK, George E, Aghayev A, et al. Implementation and Performance of Automated Software for Computing Right-to-Left Ventricular Diameter Ratio From Computed Tomography Pulmonary Angiography Images. *J Comput Assist Tomogr*. 2016;40(3):387–392. [PubMed: 26938697]
60. Dudzinski DM, Hariharan P, Parry BA, Chang Y, Kabrhel C. Assessment of Right Ventricular Strain by Computed Tomography Versus Echocardiography in Acute Pulmonary Embolism. *Acad Emerg Med*. 2017;24(3):337–343. [PubMed: 27664798]
61. Qanadli SD, El Hajjam M, Vieillard-Baron A, et al. New CT index to quantify arterial obstruction in pulmonary embolism: comparison with angiographic index and echocardiography. *AJR Am J Roentgenol*. 2001;176(6):1415–1420. [PubMed: 11373204]
62. Aviram G, Soikher E, Bendet A, et al. Automatic assessment of cardiac load due to acute pulmonary embolism: Saddle vs. central and peripheral emboli distribution. *Heart Lung*. 2016;45(3):261–269. [PubMed: 26976066]

63. Gouin B, Blondon M, Jimenez D, et al. Clinical Prognosis of Nonmassive Central and Noncentral Pulmonary Embolism: A Registry-Based Cohort Study. *Chest*. 2017;151(4):829–837. [PubMed: 27876590]
64. El-Menyar A, Nabir S, Ahmed N, Asim M, Jabbour G, Al-Thani H. Diagnostic implications of computed tomography pulmonary angiography in patients with pulmonary embolism. *Ann Thorac Med*. 2016;11(4):269–276. [PubMed: 27803753]
65. Hariharan P, Dudzinski DM, Rosovsky R, et al. Relation Among Clot Burden, Right-Sided Heart Strain, and Adverse Events After Acute Pulmonary Embolism. *Am J Cardiol*. 2016;118(10):1568–1573. [PubMed: 27742425]
66. Metter D, Tulchinsky M, Freeman LM. Current Status of Ventilation-Perfusion Scintigraphy for Suspected Pulmonary Embolism. *AJR Am J Roentgenol*. 2017;208(3):489–494. [PubMed: 28095020]
67. Investigators P. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA*. 1990;263(20):2753–2759. [PubMed: 2332918]
68. Worsley DF, Alavi A. Comprehensive analysis of the results of the PIOPED Study. Prospective Investigation of Pulmonary Embolism Diagnosis Study. *J Nucl Med*. 1995;36(12):2380–2387. [PubMed: 8523135]
69. Reinartz P, Wildberger JE, Schaefer W, Nowak B, Mahnken AH, Buell U. Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT. *J Nucl Med*. 2004;45(9):1501–1508. [PubMed: 15347717]
70. Bajc M, Olsson B, Palmer J, Jonson B. Ventilation/Perfusion SPECT for diagnostics of pulmonary embolism in clinical practice. *J Intern Med*. 2008;264(4):379–387. [PubMed: 18823506]
71. Reinartz P, Kaiser HJ, Wildberger JE, Gordji C, Nowak B, Buell U. SPECT imaging in the diagnosis of pulmonary embolism: automated detection of match and mismatch defects by means of image-processing techniques. *J Nucl Med*. 2006;47(6):968–973. [PubMed: 16741306]
72. Gutte H, Mortensen J, Jensen CV, et al. Detection of pulmonary embolism with combined ventilation-perfusion SPECT and low-dose CT: head-to-head comparison with multidetector CT angiography. *J Nucl Med*. 2009;50(12):1987–1992. [PubMed: 19910421]
73. Non-Contrast 4DCT to Detect Pulmonary Thromboembolic Events. <https://ClinicalTrials.gov/show/NCT03183063>.
74. Comparison of 3 Diagnostic Strategies of PE: Planar V/Q Scan, CTPA, and V/Q SPECT. <https://ClinicalTrials.gov/show/NCT02983760>.
75. Ohno Y, Yoshikawa T, Kishida Y, Seki S, Karabulut N. Unenhanced and Contrast-Enhanced MR Angiography and Perfusion Imaging for Suspected Pulmonary Thromboembolism. *AJR Am J Roentgenol*. 2017;208(3):517–530. [PubMed: 28075625]
76. Hatabu H, Gefter WB, Kressel HY, Axel L, Lenkinski RE. Pulmonary vasculature: high-resolution MR imaging. Work in progress. *Radiology*. 1989;171(2):391–395. [PubMed: 2704803]
77. Kluge A, Luboldt W, Bachmann G. Acute pulmonary embolism to the subsegmental level: diagnostic accuracy of three MRI techniques compared with 16-MDCT. *AJR Am J Roentgenol*. 2006;187(1):W7–14. [PubMed: 16794142]
78. Heidt T, Ehrismann S, Hovener JB, et al. Molecular Imaging of Activated Platelets Allows the Detection of Pulmonary Embolism with Magnetic Resonance Imaging. *Sci Rep*. 2016;6:25044. [PubMed: 27138487]
79. Li J, Feng L, Li J, Tang J. Diagnostic accuracy of magnetic resonance angiography for acute pulmonary embolism - a systematic review and meta-analysis. *Vasa*. 2016;45(2):149–154. [PubMed: 27058801]
80. Revel MP, Sanchez O, Couchon S, et al. Diagnostic accuracy of magnetic resonance imaging for an acute pulmonary embolism: results of the 'IRM-EP' study. *J Thromb Haemost*. 2012;10(5):743–750. [PubMed: 22321816]
81. Stein PD, Chenevert TL, Fowler SE, et al. Gadolinium-enhanced magnetic resonance angiography for pulmonary embolism: a multicenter prospective study (PIOPED III). *Ann Intern Med*. 2010;152(7):434–443, W142-433. [PubMed: 20368649]

82. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation*. 2011;123(16):1788–1830. [PubMed: 21422387]
83. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35(43):3033–3069, 3069a–3069k. [PubMed: 25173341]
84. Nagle SK, Schiebler ML, Repplinger MD, et al. Contrast enhanced pulmonary magnetic resonance angiography for pulmonary embolism: Building a successful program. *Eur J Radiol*. 2016;85(3):553–563. [PubMed: 26860667]
85. Spuentrup E, Katoh M, Wiethoff AJ, et al. Molecular magnetic resonance imaging of pulmonary emboli with a fibrin-specific contrast agent. *Am J Respir Crit Care Med*. 2005;172(4):494–500. [PubMed: 15937292]
86. Vymazal J, Spuentrup E, Cardenas-Molina G, et al. Thrombus imaging with fibrin-specific gadolinium-based MR contrast agent EP-2104R: results of a phase II clinical study of feasibility. *Invest Radiol*. 2009;44(11):697–704. [PubMed: 19809344]
87. Miserus RJ, Herias MV, Prinzen L, et al. Molecular MRI of early thrombus formation using a bimodal alpha2-antiplasmin-based contrast agent. *JACC Cardiovasc Imaging*. 2009;2(8):987–996. [PubMed: 19679287]
88. Temme S, Grapentin C, Quast C, et al. Noninvasive Imaging of Early Venous Thrombosis by 19F Magnetic Resonance Imaging With Targeted Perfluorocarbon Nanoemulsions. *Circulation*. 2015;131(16):1405–1414. [PubMed: 25700177]
89. Hosch W, Schlieter M, Ley S, Heye T, Kauczor HU, Libicher M. Detection of acute pulmonary embolism: feasibility of diagnostic accuracy of MRI using a stepwise protocol. *Emerg Radiol*. 2014;21(2):151–158. [PubMed: 24282047]
90. Garcia-Alvarez A, Fernandez-Friera L, Garcia-Ruiz JM, et al. Noninvasive monitoring of serial changes in pulmonary vascular resistance and acute vasodilator testing using cardiac magnetic resonance. *J Am Coll Cardiol*. 2013;62(17):1621–1631. [PubMed: 23954344]
91. Brooks RA. A quantitative theory of the Hounsfield unit and its application to dual energy scanning. *J Comput Assist Tomogr*. 1977;1(4):487–493. [PubMed: 615229]
92. Ferda J, Ferdova E, Mirka H, et al. Pulmonary imaging using dual-energy CT, a role of the assessment of iodine and air distribution. *Eur J Radiol*. 2011;77(2):287–293. [PubMed: 19717260]
93. Bauer RW, Frellesen C, Renker M, et al. Dual energy CT pulmonary blood volume assessment in acute pulmonary embolism - correlation with D-dimer level, right heart strain and clinical outcome. *Eur Radiol*. 2011;21(9):1914–1921. [PubMed: 21533631]
94. Meysman M, Everaert H, Buls N, Nieboer K, de Mey J. Comparison of ventilation-perfusion single-photon emission computed tomography (V/Q SPECT) versus dual-energy CT perfusion and angiography (DECT) after 6 months of pulmonary embolism (PE) treatment. *Eur J Radiol*. 2015;84(9):1816–1819. [PubMed: 26074385]
95. Lu GM, Zhao Y, Zhang LJ, Schoepf UJ. Dual-energy CT of the lung. *AJR Am J Roentgenol*. 2012;199(5 Suppl):S40–53. [PubMed: 23097167]
96. Hwang HJ, Hoffman EA, Lee CH, et al. The role of dual-energy computed tomography in the assessment of pulmonary function. *Eur J Radiol*. 2017;86:320–334. [PubMed: 27865580]
97. Okada M, Kunihiro Y, Nakashima Y, et al. Added value of lung perfused blood volume images using dual-energy CT for assessment of acute pulmonary embolism. *Eur J Radiol*. 2015;84(1):172–177. [PubMed: 25445893]
98. Le Faivre J, Duhamel A, Khung S, et al. Impact of CT perfusion imaging on the assessment of peripheral chronic pulmonary thromboembolism: clinical experience in 62 patients. *Eur Radiol*. 2016;26(11):4011–4020. [PubMed: 26976297]
99. Chang S, Hur J, Im DJ, et al. Dual-energy CT-based iodine quantification for differentiating pulmonary artery sarcoma from pulmonary thromboembolism: a pilot study. *Eur Radiol*. 2016;26(9):3162–3170. [PubMed: 26638163]

100. Kline JA, Mitchell AM, Kabrhel C, et al. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. *J Thromb Haemost* 2004; 2(8):1247–55. [PubMed: 15304025]
101. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med* 2001;135(2): 98–107. [PubMed: 11453709]
102. Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med* 2006;144(3):165–71. [PubMed: 16461960]

Synopsis:

Imaging continues to be the modality of choice for the diagnosis of venous thromboembolic disease, particularly when incorporated into diagnostic algorithms. Improvement in imaging techniques as well as new imaging modalities and processing methods have improved diagnostic accuracy and additionally are being leveraged in prognostication and decision making for choice of intervention. In this manuscript, we review the role of imaging in diagnosis and prognostication of venous thromboembolism. We also discuss emerging imaging approaches that may in the near future find clinical utility in improving diagnosis and prognostication as well as differentiating disease phenotypes.

Figure 1. Ultrasound evidence of DVT at bifurcation of R popliteal Vein. (A) Demonstration of partially occlusive thrombus in R popliteal vein and accompanying color flow doppler (B) showing decreased flow in R popliteal vein. Spectral waveforms measuring the velocity of flow demonstrate an increase in velocity during an augmentation (marked by the yellow star) (C) consistent with presence of residual flow.

Figure 2.
Suspect Acute PE Algorithm

Figure 3:

Three examples of pulmonary angiography in acute pulmonary embolus. An Area of lucency can be seen (example blue arrow) where a clot is blocking flow leading to decreased opacification of the pulmonary vascular tree on the right compared to the left. Complete occlusion of flow is noted on the middle panel with minimal opacification of the lower lobes on the left. Bilateral pulmonary emboli on the rightmost panel demonstrating “cut offs” and minimal flow beyond the central pulmonary artery.

Figure 4: Examples of CT findings in Acute Pulmonary Embolism

From top left: Example of Saddle PE, Example of Lobar PE, Example of Doughnut Sign

Second row: Example of a saddle embolus, with corresponding RV dilation and heterogeneous perfusion of the lung

Third row: Vascular reconstruction of the subject from the second row demonstrating areas with decreased detection of vessels corresponding to the areas of decreased perfusion as compared to a normal subject (right panel).

Figure 5:

Magnetic resonance imaging without IV contrast due to impaired kidney function in a 65-year-old man. Scanning using axial Half-Fourier Acquisition Single-shot Turbo spin Echo imaging (HASTE); and axial, sagittal and coronal True fast imaging with steady state precession (TRUE FISP). There is a filling defect in the main left pulmonary artery extending into the ascending and descending branches (arrows).

Figure 6.

Images from a Dual energy CT. a) Mixed CT image in mediastinal window setting shows occlusive thrombi in both lower lobar pulmonary arteries . Also noted is right atrial thrombus (arrow). b and c) Axial and coronal Perfused Blood Volume (PBV) images demonstrate large wedge shaped perfusion defects in both lungs, most severe in lower lobes. d) Lung Vessel Image shows distribution of iodine containing and non-opacified pulmonary arteries. The iodine containing pulmonary arterial branches are coded in blue, while the non-opacified arteries are coded in red.

Courtesy of Rahul Renapurkar, MD.