Novel imaging strategies in venous thromboembolism
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CHAPTER

General discussion and summary

In this thesis, we described studies that aimed to overcome diagnostic challenges in venous thromboembolism (VTE) using novel imaging techniques. **Chapter 1** provides a general introduction of the diagnosis of pulmonary embolism (PE) and deep vein thrombosis (DVT) at different anatomic locations and an overview of the presented studies.

The diagnostic management of suspected VTE can be complex, especially in certain settings such as in suspected recurrent VTE. An adequate diagnosis in this patientgroup is of great importance because most patients diagnosed with a recurrence are treated with lifelong anticoagulant treatment. In suspected recurrent PE, the YEARS algorithm incorporating 3 clinical items and a D-dimer test with a pre-test probability dependent threshold, followed by computed tomography pulmonary angiography (CTPA) is the current favored diagnostic strategy. Although persistent thrombi can be present after a previous PE, these are hardly relevant in the diagnostic management of suspected recurrent PE. In most patients the PE will completely resolve over time and when persistent thrombi in the pulmonary artery are present these are often of limited size.

The diagnostic management in suspected recurrent DVT proves more of a challenge. First, the safety of the commonly used Wells score in combination with a D-dimer test in this setting has not been proven beyond doubt. Second, up to 50% of patients with a previous DVT have persistent thrombi after one year, despite adequate anticoagulant treatment. The differentiation between acute recurrent DVT and chronic residual thrombosis with compression ultrasonography (CUS) is difficult and sometimes impossible. As a result, CUS is not able to provide a definite diagnosis in 30% of patients with suspected recurrent ipsilateral DVT. Magnetic Resonance Non-Contrast Thrombus Imaging (MR-NCTI) is a magnetic resonance imaging (MRI) technique that can directly visualize the metabolism of a fresh thrombus by imaging methemoglobin, which is formed in a fresh blood clot by the oxidation of hemoglobin. This technique can thus be used to differentiate acute from chronic thrombosis and to accurately visualize notorious difficult to image VTE. Magnetic Resonance Direct Thrombus Imaging (MRDTI) is a MR-NCTI sequence that has been shown to accurately diagnosis a first DVT and to differentiate acute from chronic DVT in the legs. Before MRDTI could be implemented in the diagnostic management of suspected recurrent ipsilateral DVT in clinical practice an outcome study needed to be performed.

In **Chapter 2**, we described the Theia study in which the safety of MRDTI to exclude acute recurrent ipsilateral DVT was assessed. We showed that the 3-month incidence of recurrent VTE was low in patients with MRDTI negative for DVT (1.1%; 95% confidence interval (95%CI) 0.13-3.8) and in patients with MRDTI negative for DVT and thrombophlebitis, who were not treated with any anticoagulant during follow-up (1.7%; 95%CI 0.20-5.9). Moreover, with an excellent interobserver agreement and MRDTI not being available in only 3.6% of patients, this technique was proven to be a feasible and reproducible diagnostic test. Additionally, the use of MRDTI possibly resulted in 19% fewer false positive diagnoses. However, as a MRI scan is more expensive than a CUS examination, the cost-effectiveness of the addition of MRDTI to the diagnostic management of suspected recurrent DVT needed to be proven before this technique can be widely implemented. In **Chapter 3**, the one-year healthcare costs of 10 diagnostic strategies including the Wells score in combination with a D-dimer test, CUS and/or MRDTI in suspected recurrent DVT was assessed and compared. We showed that the healthcare costs of strategies with MRDTI were generally lower than of strategies without MRDTI, due to superior specificity resulting in less false-positive diagnosis and overtreatment. Therefore, it was concluded that application of MRDTI to the diagnostic management of suspected recurrent ipsilateral DVT will not increase healthcare costs.

Healthcare costs can also be reduced with the use of diagnostic algorithms in which VTE can be ruled out without additional imaging tests, i.e. in case of a low clinical probability in combination with a negative D-dimer test. As discussed, the safety of these algorithms has not yet been proven in large prospective studies exclusively in patients with suspected recurrent DVT. In **Chapter 4**, we therefore evaluated the diagnostic accuracy of the combination of the (modified) Wells rule for DVT and D-dimer for suspected recurrent ipsilateral DVT in the prospective Theia study. We showed that excluding recurrent DVT based on a low clinical probability according the (modified) Wells rule in combination with a negative D-dimer test would have resulted in an unacceptable high failure-rate (6.1-11%). Our data therefore suggest not to routinely apply assessment of a clinical decision rule and D-dimer in the diagnostic workup of suspected recurrent DVT, but to directly perform a CUS to exclude or diagnose recurrent DVT. In patients with a suspected recurrent ipsilateral DVT and inconclusive CUS, MRDTI should be performed to provide a definitive diagnosis.

The diagnostic management of upper extremity deep vein thrombosis (UEDVT) is also very challenging due to the anatomic location of the deep veins. Adequate visualization is difficult as the upper extremity deep veins lies partly within the thoracic cavity. Moreover, CUS examination is hindered due to overlying bone structures, such as the claviculae. We hypothesized that MR-NCTI would be an accurate diagnostic test without the invasive characteristics of (CT) venography imaging. MRDTI and T1-weighted Turbo Spin-echo Spectral Attenuated Inversion Recovery, which is another MR-NCTI sequence, were previously shown to successfully visualize acute thrombosis in three patients with UEDVT proven by conventional imaging. In **Chapter 5**, the results of the Selene study were described in which the diagnostic accuracy of MR-NCTI for the diagnosis of UEDVT was evaluated. We showed that MR-NCTI was accurate with a sensitivity of 93% (95%CI 78-99%) and specificity of 100% (95%CI 88-100%) and had an excellent interobserver agreement. This technique may therefore be useful in patients with suspected UEDVT but with inconclusive CUS.

Differentiation between acute and chronic thrombosis is also important in the diagnostic management of portal vein thrombosis (PVT), as current guidelines recommend different anticoagulant strategies in patients with acute or chronic PVT. With currently available imaging tests including doppler ultrasonography, CT venography and MRI, this is not always possible, especially in case of an organized non-occlusive chronic PVT without signs of cavernous transformation of the portal vein. We hypothesized that MR-NCTI could accurately differentiate acute from chronic PVT. In **Chapter 6**, the first phase of the Rhea study was described, in which we evaluated the most optimal MR-NCTI sequences for the setting of PVT. We found that three-dimensional (3D) T1 Turbo Field Echo and 3D T1 Dixon Fast Field Echo were both able to diagnose and differentiate acute from chronic PVT. These MR-NCTI sequences will therefore be evaluated in the second phase of the Rhea study to assess its diagnostic accuracy for distinguishing acute from chronic PVT.

The diagnosis of cerebral vein thrombosis (CVT) can also be challenging due to the complex anatomic variation of cerebral veins and sinuses. Digital subtraction angiography was previously the diagnostic standard for CVT but is now rarely used due to its invasive nature. In **Chapter 7**, an overview of all relevant papers regarding the diagnostic performance of the current available imaging techniques including CT, CT venography and MRI for the diagnosis of CVT is presented. Although large high-quality diagnostic studies are absent, we showed that contrast-enhanced imaging techniques are more accurate than non-contrast-enhanced techniques. We also described that CT venography and contrast-enhanced MRI both seem adequate for the diagnosis of CVT. MR-NCTI was previously shown to be accurate for the diagnosis of CVT too. Therefore, MR-NCTI could possibly be of value in establishing a final diagnosis in complex cases, such as in patients with suspected recurrent CVT and in patients in whom venous sinuses are affected by brain tumours or after intracranial surgery. In **Chapter 8**, we described a 52-year-old female patient who presented at the Emergency Department with a mild headache and blurry vision and was suspected of an acute CVT. Her medical history included a craniotomy for right sided parieto-occipital meningioma. Imaging with CT and MR venography showed no opacification of the superior sagittal sinus and both transverse sinuses suspected of thrombosis, but of unknown age. However, as MR-NCTI showed no high signal intensity, acute CVT was excluded and anticoagulant treatment discontinued. The cerebral sinus occlusion was most likely due to chronic CVT or as a result of residual meningioma tissue and follow-up MRI showed no new abnormalities, nor had the patient new adverse events during 12 months of follow-up. MRDTI also excluded an acute thrombus in a patient with aortic thrombosis. This case was described in **Chapter 9**. It concerned a 43-year-old male patient known with severe hypertension and renal failure, who presented with abdominal pain for several months. CT angiography showed a large extensive circumferential wall thrombosis in an abdominal aortic aneurysm. The patient was referred for MRDTI scan, since it was unknown whether the thrombus concerned an acute or chronic thrombosis, and the treating doctors were hesitant to start anticoagulant treatment because of the high bleeding risk. MRDTI excluded an acute thrombus, and anticoagulant treatment was not started. These two case reports represent the first cases in which MR-NCTI techniques were used to guide anticoagulant treatment in suspected acute CVT and aortic thrombosis.

CTPA is the diagnostic test of choice for the diagnosis of acute PE. Moreover, CTPA parameters of right heart dysfunction, including right ventricle to left ventricle diameter ratio (RV/LV ratio) and pulmonary artery trunk diameter, can be used in the initial risk stratification of acute PE patients. A novel CT technique, called CT pulmonary perfusion (CTPP), has an added value to CTPA reading as it shows the pulmonary perfusion and thus possible functional impact of an acute PE. CTPP has previously be shown to improve the diagnosis of PE when added to CTPA. We hypothesized that CTPP could also improve the prediction of adverse outcomes of PE. In **Chapter 10,** we evaluated the correlation between perfusion defect score (PDS) on CTPP and both clinical presentation and adverse short-term outcomes in hemodynamically stable PE patients. In this analysis, we were not able to show an association between PDS and clinical presentation such as chest pain, dyspnea and haemoptysis. We did show that PDS was correlated to the need for reperfusion therapy and PE-related mortality.

Perfusion defect quantification may not only be clinically relevant for initial risk stratification of acute PE, but possibly also for prediction of long-term adverse outcomes. Extensive clot burden and perfusion defects at the moment of a PE diagnosis have been associated with residual perfusion defects and with persistent symptoms. Therefore, we hypothesized that the extent of perfusion defects as measured by CTPP at PE diagnosis would predict persistent symptoms and 3-month adverse outcomes, including recurrent PE, PE-related readmission and all-cause mortality. In **Chapter 11**, we showed that PDS on CTPP at initial PE diagnosis was not associated to persistent symptoms nor to any of the three adverse outcomes. Future larger studies are needed to determine the value of CTPP to CTPA for the prognostic management of acute PE patients.

The year 2020 was characterized by the coronavirus disease 19 (COVID-19) outbreak which has led to worldwide spreading of a highly infectious respiratory disease caused by a new coronavirus known as SARS-CoV-2. COVID-19 infection has been associated with an increased incidence of VTE and in particular PE. However, the pathogenesis of COVID-19 associated PE is currently not fully understood. It has been suggested that these pulmonary emboli may be the result of in-situ immunothrombosis rather than conventional VTE. This hypothesis was based on the results of autopsy studies in patients with COVID-19 pneumonia showing multiple small thrombi in the alveolar capillaries. To test this hypothesis, we assessed the clinical and CT characteristics of PE in patients with COVID-19 and compared these to the characteristics of PE in patients without COVID-19. In **Chapter 12**, we showed that the PE in patients with COVID-19 was less extensive and more located in the peripheral lung segments. Also, the mean RV/LV ratio was lower in COVID-19 patients, as was the prevalence of RV/LV ratio >1. We therefore concluded that COVID-19 associated PE is indeed different from conventional PE, a finding that could support the in-situ immunothrombosis theory. This also suggests a possible different (prophylactic) anticoagulant strategy in this patient group then the conventional VTE treatment. Future studies to the exact pathophysiology of COVID-19 associated PE and most optimal anticoagulant treatment are needed.

FUTURE PERSPECTIVES

Major technical advances have been made in the diagnostic imaging of VTE. This has led to an increase in the detection of very small and/or incidental thrombi. The clinical relevance and most optimal treatment of these thrombi is often not known. With the introduction of MR-NCTI, we are able to directly visualize thrombosis and differentiate acute from chronic thrombosis, and with that determine the need for anticoagulant treatment. In suspected recurrent ipsilateral DVT, MR-NCTI is now increasingly used when a recurrence cannot be diagnosed or excluded with CUS. Formally a diagnostic outcome study on the safety of MR-NCTI for excluding UEDVT and CVT is needed before this technique can be implemented in these settings as well. Of note, when translating the findings of the Theia study to suspected UEDVT and CVT, MR-NCTI may be applied in complex clinical cases in which non-invasive diagnostic tests do not provide a definitive diagnosis, even in the absence of such a study.

In splanchnic vein thrombosis (SVT), MR-NCTI could be used to guide the treatment decision in patients with suspected chronic SVT as current guidelines suggest no anticoagulation in patients with chronic rather than acute SVT. Therefore, when the accuracy of MR-NCTI for the differentiation between acute and chronic SVT has been proven in the Rhea study, an outcome study should be performed, ideally in a randomized controlled trial (RCT), in which patients with suspected chronic SVT and normal MR-NCTI will be randomized between therapeutic anticoagulant treatment and no anticoagulation to compare clinical outcome, i.e. the occurrence of recurrent or progressive SVT, major bleeding and death. This will be particularly relevant for patients with incidental SVT, a group of patients comprising 30% of all SVTs, even when conventional imaging tests do not indicate signs of chronicity.

Before MR-NCTI can be widely implemented in daily clinical practice when its safety has been proven in diagnostic outcome studies, implementation challenges in real-world practice need to be assessed and addressed. Among those are the lower availability of and less experience with MR-NCTI compared to conventional VTE imaging techniques. Moreover, MRI is associated with higher imaging costs. Therefore, implementation studies are needed to develop the most optimal strategies to include MR-NCTI in daily clinical practice. These studies should among others focus on the exact indications of MR-NCTI imaging, the training of MR technicians and radiologist, the latter who have to learn to interpret MR-NCTI images.

In the diagnostic management of suspected PE, CTPP and ventilation/perfusion single photon emission computed tomography (V/Q SPECT) scintigraphy can both provide lung perfusion images, however their place in the diagnostic and prognostic management of PE is still yet to be determined. Indeed, while MR-

NCTI is close to implementation in practice, this is not the case for CTPP. For instance, as manual perfusion defect quantification is time-consuming and current literature does not unambiguously support the added value of perfusion imaging on top of CTPA, its applicability in daily clinical practice is still unknown. With the development and validation of artificial intelligence-based (AI) software it may be possible to more accurately and reproducible quantify perfusion defects. Automatically quantification of perfusion defects, if shown more reliably associated with prognosis, could in turn facilitate implementation of CTPP in daily practice, allowing for precision management with regard to initial treatment, duration of hospitalization and patient tailored follow-up. Studies to achieve this are currently ongoing.