From the Department of Physiology and Pharmacology
Karolinska Institutet, Stockholm, Sweden

Current diagnostic aspects on acute and chronic pulmonary embolism:

MRI in acute pulmonary embolism, CT in chronic thromboembolic pulmonary hypertension and what the radiologists actually know.

Anna Nordgren Rogberg

Karolinska Institutet

Stockholm 2020

The cover image is part of an illustration by Rudolf Tupy © Kooperativa Förbundet (KF)

All previously published papers were reproduced with permission from the publisher.

Published by Karolinska Institutet.

ISBN 978-91-7831-737-0

Printed by Eprint AB 2020

INSTITUTIONEN FÖR FYSIOLOGI OCH FARMAKOLOGI

CURRENT DIAGNOSTIC ASPECTS ON ACUTE AND CHRONIC PULMONARY EMBOLISM:

MRI in acute pulmonary embolism, CT in chronic thromboembolic pulmonary hypertension and what the radiologists actually know.

AKADEMISK AVHANDLING

Som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligt försvaras i Föreläsningssal "Hjärtat", plan 5, Hus 18, Danderyds sjukhus.

Fredagen den 8 maj, 2020, kl 09.00

Av

Anna Nordgren Rogberg

Principal Supervisor:
Associate Professor Peter Lindholm
Karolinska Institutet
Department of Physiology and Pharmacology

Co-supervisors:
Associate Professor Sven Nyrén
Karolinska Institutet
Department of Molecular Medicine and Surgery
Division of Diagnostic Radiology

MD PhD Eli Westerlund
Karolinska Institutet
Department of Clinical Sciences,
Danderyds Hospital

Opponent:
MD PhD Thomas Hansen
Uppsala University
Department of Surgical Sciences
Division of Radiology

Examination Board:
Professor Margareta Holmström
Linköping University
Department of Health, Medicine and Caring Sciences
Division of Diagnostics and Specialist Medicine

Associate Professor Torkel Brismar
Karolinska Institutet
Department of Clinical Science, Intervention and Technology CLINTEC
Division of Radiology

Associate Professor Anna Kiessling
Karolinska Institutet
Department of Clinical Sciences,
Danderyds Hospital

To Jonas, John and Lovisa

and

to Louise, Gunnar, Görel and Jan for their love and support.

ABSTRACT

Background: Acute pulmonary embolism (APE) is a potentially severe medical condition with blood clots obstructing the pulmonary arterial vasculature. In most cases the APE resolves without any sequelae after anticoagulation therapy. In some patients, however, the emboli do not resolve upon treatment and the remnants cause increased vascular resistance, a condition known as chronic thromboembolic pulmonary hypertension (CTEPH). Both APE and CTEPH have a non-specific clinical presentation and imaging is an important part of the diagnosis. In APE computed tomography pulmonary angiography (CTPA) is the diagnostic gold standard, although the method is not suitable for all patients. CTPA has a high specificity for CTEPH, but the sensitivity remains under debate. At present CTPA is not recommended as a first line test among patients with a clinical suspicion of CTEPH.

Purpose: To investigate unestablished imaging modalities in the diagnosis of APE (*Study I*) and CTEPH (*Study III*) including learning aspects (*Study II*) and knowledge (*Study IV*) of theses among radiologists. Regarding APE we studied magnetic resonance imaging (MRI) and in CTEPH we studied CTPA.

Material and methods: *Studies I-II* were based on a prospective collection of 70 unenhanced MRI exams with CTPA as the gold standard. In *Studies III-IV* we used a retrospective material based on 43 CTPA exams from patients with confirmed CTEPH referred for pre-surgical assessment at a specialist centre, with a matched control with suspected APE.

Results: All MRI exams were of diagnostic quality. Specificity was 100% for both readers and sensitivity 90% and 93% respectively with a nearly perfect inter-reader agreement (kappa 0.97) (*Study I*). Residents interpreting the MRI exams within the training program reached a clinically acceptable level after approximately 50 examinations and review time was halved during the training program (*Study II*). The sensitivity for CTEPH on CTPA reviewed by two experts was 100% and the specificity 100% (*Study III*), while the sensitivity based on the original reports from the same cases was 26% (*Study IV*).

Conclusions: Unenhanced MRI has a high sensitivity and specificity for APE (*Study I*) and residents can learn to interpret such exams by using a self-directed training program (*Study II*). Enhanced CTPA has a high sensitivity when reviewed by experienced radiologists (*Study III*), but among radiologists in general the sensitivity is low (*Study IV*).

LIST OF SCIENTIFIC PAPERS

I. Detection of pulmonary embolism using repeated MRI acquisitions without respiratory gating: A preliminary study.[1]
Nyrén S*, **Nordgren Rogberg A**, Vargas Paris R, Bengtsson B, Westerlund E, Lindholm P
Acta Radiol. 2017 Mar;58(3):272-278

II. How to train radiology residents to diagnose pulmonary embolism using a dedicated MRI protocol
Nordgren Rogberg A*, Nyrén S, Westerlund E, Lindholm P
Acta Radiol Open. 2017 Sep 27;6 (9): 2058460117734244

III. Sensitivity of computed tomography pulmonary angiography for diagnosing chronic thromboembolic pulmonary hypertension
Nordgren Rogberg A*, Gopalan D, Westerlund E, Nyrén S, Lindholm P
Manuscript 2020

IV. Do radiologists detect chronic thromboembolic disease on computed tomography?
Nordgren Rogberg A*, Gopalan D, Westerlund E, Lindholm P.
Acta Radiol. 2019 Nov;60 (11):1576-1583

* Indicates the Corresponding Author.

[1]*Awarded* **Xenia Fosselliana Prize 2017** as the best scientific article from a Nordic institution published in Acta Radiologica 2017.

CONTENTS

LIST OF ABBREVIATIONS

AA	Ascending aorta
APE	Acute pulmonary embolism
CT	Computed tomography
CTED	Chronic thromboembolic disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomography pulmonary angiography
DSA	Digital subtraction angiography
ESC	European Society of Cardiology
MRA	Magnetic resonance angiography, (gadolinium-enhanced)
GGOs	Ground glass opacities
HRCT	High resolution computed tomography
mPAP	Mean pulmonary arterial pressure
MRI	Magnetic resonance imaging
MPA	Main pulmonary artery
NPV	Negative predictive value
PACS	Picture archiving and communication system
PEA	Pulmonary endarterectomy
PH	Pulmonary hypertension
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
PPV	Positive predictive value
RA	Right atrium
RV	Right ventricle
RVH	Right ventricular hypertrophy
SSFP	Steady-state free precession
V/Q scan	Ventilation-perfusion scintigraphy
95% CI	95% confidence interval

1 INTRODUCTION

Deep venous thrombosis (DVT) and acute pulmonary embolism (APE) are different manifestations of the same disease, usually referred to as venous thromboembolism (VTE). VTE is usually caused by a combination of hypercoagulability, stasis of blood flow and endothelial damage usually referred to as the triad of Virchow (1). APE usually originates from a thrombosis in the deep veins of the leg that has migrated to the pulmonary arteries. After myocardial infarction and stroke, APE is the third most common cause of death from cardiovascular disease (2). Imaging is an essential part of the diagnostic work-up, since the clinical presentation of APE is non-specific (3). Computed tomography pulmonary angiography (CTPA) is presently the primary radiological investigation in clinical practice and has recently been accepted as the gold standard within research (4, 5). CTPA has a high sensitivity and specificity for APE, it is widely available and the acquisition time is short. However, the administration of iodinated contrast media and the exposure to ionising radiation are potential limitations (6). Recent technical improvements suggest magnetic resonance imaging (MRI) as an option when CTPA is contraindicated, but it is not fully accepted as a diagnostic method for APE as yet (6, 7).

In most patients with APE the emboli resolve without any sequelae. However, in some patients the embolus does not resolve but develop into endothelial fibrotic obstructions. The results are increased vascular resistance, pulmonary hypertension (PH) and right heart failure (8, 9), a condition known as chronic thromboembolic pulmonary hypertension (CTEPH). The cause of this process remains unknown (8, 9), but associated conditions are thrombophilic disorders and splenectomy (10). The clinical manifestation is usually non-specific and associated with the PH. It is important to distinguish CTEPH from other forms of PH since it is the only one that can be cured (11), but for a number of reasons the diagnosis is often delayed (12, 13).

The rapid development in radiology in response to the current technical development requires a continuous training throughout the career among radiologists. However, the expertise on how to train radiology residents is limited (14) and the availability of continuous learning programs for radiologists even more so. These aspects are of great importance when introducing new diagnostic methods.

2 BACKGROUND

2.1 EPIDEMIOLOGY

2.1.1 APE

Most data on epidemiology, risk factors and natural history of APE is based on studies investigating the entire entity of VTE (4). According to the 2019 European Society of Cardiology (ESC) guidelines on the diagnosis and management of APE, the annual incidence of APE has been estimated to be 39-115 per 100 000 people (15). In Sweden, the incidence of PE in 2004 was 20-60 per 100 000 and 10-15 per 100 000 lethal APE incidences determined by autopsy (16). However, the incidence has increased in many countries in recent years due to improved diagnostics; in Sweden for example, the National Board of Health and Welfare's database indicates an increase from 43 to 64 per 100 000 patients admitted to hospital due to PE between the years 2004 and 2018 (17).

The mortality rate in APE differs from >15% in haemodynamically unstable patients, 3-15% in intermediate risk patients with right ventricular dysfunction or myocardial damage and <1% in low risk patients (18). This indicates the importance of distinguishing the relatively small group of haemodynamically unstable high-risk patients from the normotensive intermediate- or low-risk patients (18, 19).

There is no agreement on whether VTE varies according to gender (2). In young patients, however, there seems to be a female predominance, probably due to hormonal factors such as oral contraceptives and pregnancy (16). VTE can be provoked by reversible risk factors such as surgery, trauma, immobilisation, pregnancy and hormonal treatments up to three months prior to diagnosis (4). Malignancy is also a major risk factor although the risk of VTE varies with different types and stages of cancer: Pancreas, gynaecological, lung, stomach, kidney and primary brain cancer showing the highest risk (20, 21). The existence of reversible risk factors is important since it is taken into consideration regarding duration of anticoagulation therapy, which according to current recommendations is either three months or indefinitely (22).

2.1.2 CTEPH

CTEPH was previously considered to occur in 0.1– 0.5% of APE survivors (23). However, more recent studies indicate that it is a rather common complication of APE ranging from 2.8% and 4.8% with most cases occurring within two years of the initial event (23-25). It should also be noted that about 25% of CTEPH patients have no previously known history of VTE according to the International CTEPH Registry (26). Risk factors for developing CTEPH include thrombophilic disorders seen in 32% and splenectomy reported in 3.4% of CTEPH patients, both genders are equally affected (10).

2.2 CLINICAL PRESENTATION

2.2.1 APE

The clinical presentation of APE is nonspecific but includes symptoms like chest pain, cough, dyspnoea, fever, hemoptysis, tachycardia or even cardiogenic shock. Chest pain is relatively common and caused by pleural irritation associated with infarction due to peripheral emboli. Central or extensive embolization may present with haemodynamic instability or syncope. However, sometimes APE occurs as an incidental finding on computed tomography (CT) in asymptomatic patients.

2.2.2 CTEPH

The symptoms of CTEPH are nonspecific and other more common causes are usually considered first, leading to delayed diagnosis and treatment (27). The clinical presentation usually reflects the degree of PH (8, 11). Among the symptoms described are exertional dyspnoea, atypical chest pain, chronic non-productive cough, tachycardia, syncope and cor pulmonale (8). The clinical presentation may resemble APE (10) and additional acute embolisation may also occur in patients with CTEPH 'acute on chronic', which makes things more complicated. Knowledge of risk factors and clinical presentation of APE as well as CTEPH is important for the radiologist when protocolling and reading examinations.

2.3 DIAGNOSTIC METHODS

Because of the nonspecific clinical presentation of APE, imaging is an essential part of the diagnostic work up. Since the 1990s there has been a shift from invasive investigations such as phlebography and pulmonary angiography to non-invasive examinations such as venous compression ultrasonography and CTPA (9). During the last few decades there has been a constant increase in CT utilisation, including a 5-fold increase in CTPA in patients with suspected APE between 2001-2009 (28). The proportion of CTPA exams positive for APE is approximately 20% (29), but recent studies from the USA indicate that less than 10% of patients referred for CTPA actually have APE (28). Consequently there has been an increase in radiation exposure as well as health care costs why diagnostic algorithms have been developed including clinical probability assessment tests and D-dimer (28).

The diagnostic work up in CTEPH is more complicated than in APE. The 2015 ESC/ERS guidelines have presented a diagnostic algorithm for PH-patients. The first step is to perform echocardiography if PH is present. If suggestive of PH, the second step is to identify the clinically common PH groups 2 and 3 (left heart disease and lung disease respectively). At this point, some sort of imaging is usually performed, such as chest X-ray or high resolution computed tomography (HRCT). If these are negative the third step is to screen for group 4 PH (CTEPH) using V/Q scan. If positive, it is recommended to refer patients to an expert

centre for further evaluation with right heart catheterisation, CTPA and potentially pulmonary angiography. (10)

2.3.1 Clinical probability assessment tests

It is important to distinguishing high-risk patients (signs of cardiogenic shock or hypotension) from low-risk patients (haemodynamically stable patients) (15). High-risk patients are recommended immediate CTPA, while low-risk patients are further evaluated with clinical probability tests combined with D-dimer to decide if CTPA is required.

Table 1a	
Wells Score	
Parameter	**Points**
Previous VTE	1.5
Heart rate >100 b.p.m.	1.5
Surgery or immobilisation last 4 weeks	1.5
Haemoptysis	1
Active cancer	1
Clinical signs of DVT	3
Alternative diagnosis less likely than APE	3
Three-level score	
Low	0-1
Intermediate	2-6
High	>6
Two-level score	
APE unlikely	0-4
APE likely	>4

Table 1b	
Simplified Geneva Score	
Parameter	**Points**
Previous VTE	1
Heart rate 75-94 b.p.m	1
Heart rate >95 b.p.m	2
Surgery or fracture last month	1
Hemoptysis	1
Active cancer	1
Unilateral lower limb pain	1
Pain or oedema lower limb	1
Age >65 years	1
Three-level score	
Low	0-1
Intermediate	2-4
High	>4
Two-level score	
APE unlikely	0-2
APE likely	>2

Table 1. *a) Wells score parameters including the two- and three-category prediction. b) The simplified Geneva score with the two- and three-category prediction.*

Individual symptoms have limited sensitivity and specificity for APE, but the combination of findings and risk factors allows classification of patients with suspected APE into different risk categories according to the ESC guidelines 2019 (15) . The most commonly used clinical probability assessment test is the Wells score (30) where there exists both a three-category prediction (low, moderate or high probability of APE) and a two-category prediction (APE likely or unlikely), table 1a. The simplified Geneva score is also commonly used table 1b.

Both assessment tests have been adequately validated and regardless of which is used, approximately 10% in the low risk or unlikely category will have APE (15). Although, it should be noted that neither the Wells score or the simplified Geneva score accounts for estrogen related risk factors such as oral contraceptives, pregnancy or the initial postpartum period (first eight weeks after delivery) and has not been evaluated for these patients (31). However, the recent YEARS-study shows promising results for reducing diagnostic imaging also among pregnant women (32). According to the YEARS algorithm APE is ruled out if none of the criteria (clinical signs of DVT, hemoptysis and APE as the most likely diagnosis) were positive in combination with a D-dimer level less than 1000 ng per milliliter or if one or several of the criteria were positive in combination with a d-dimer less than 500 ng per milliliter.

2.3.2 D-dimer

D-dimer is used as a laboratory investigation measuring a fibrin degradation product, which increases in cases of fibrinolysis thereby suggesting the presence of thrombosis. It has a high sensitivity for VTE, but the specificity is low (33). Increased D-dimer levels can also be seen in infections, inflammatory diseases, malignancies, pregnancy and liver failure. D-dimer levels also increase with age, reducing the usefulness of the test in elderly patients (34). For instance, D-dimer testing has been able to rule out APE in 51% of patients younger than 40 years, but in no more than 5% of patients older than 80 years (35). In 2014 Righini et al presented the idea of age-adjusted D-dimer cut-off levels that actually resulted in a 5-fold increase in the proportion of patients older than 75 years where APE could safely be ruled out without any further investigations (34). Since then, age-adjusted cut-off levels regarding D-dimer has been introduced in Swedish laboratories.

To summarise, D-dimer and clinical probability tests can be used to exclude APE in approximately 30% of patients with low or intermediate risk (18). Nevertheless, in patients with a high clinical probability or elevated D-dimer, further investigations are required.

2.3.3 Pulmonary angiography

In 1938 a first attempt was made to visualise the cardiovascular system by an intravenous injection of iodine, but it was not until the mid-1960s more extensive research was made, including both intravenous contrast administration and selective pulmonary arterial angiography (36). For a long period of time pulmonary angiography was considered the gold standard of APE imaging (6, 37), although it recently has been replaced by CTPA (36, 38). In CTEPH patients on the other hand, it remains the gold standard for confirming the diagnosis (39).

Pulmonary angiography is an invasive method where a catheter is placed into the main pulmonary arterial branches, with repeated contrast injections. Angiographic findings in APE include intraluminal filling defects, arterial cut-off, areas of oligemia and asymmetric flow (36). The most common findings in CTEPH are pouch defects, intimal irregularities, abrupt vessel narrowing and bands/webs (39). The invasive nature entails complications, with reported morbidity and mortality rates ranging from 3.5–6 % and 0.2–0.5 respectively (33, 40).

It should be noted that 1.6% of patients with a normal pulmonary angiogram develop APE during a one year period, half of them within eight days (41). Furthermore, the interreader agreement on the subsegmental level is moderate, indicating limited diagnostic accuracy in small arterial branches (37, 42).

In clinical practice conventional angiography is rarely used in patients with suspected APE but is recommended as part of the pre-surgical assessment in CTEPH patients (10).

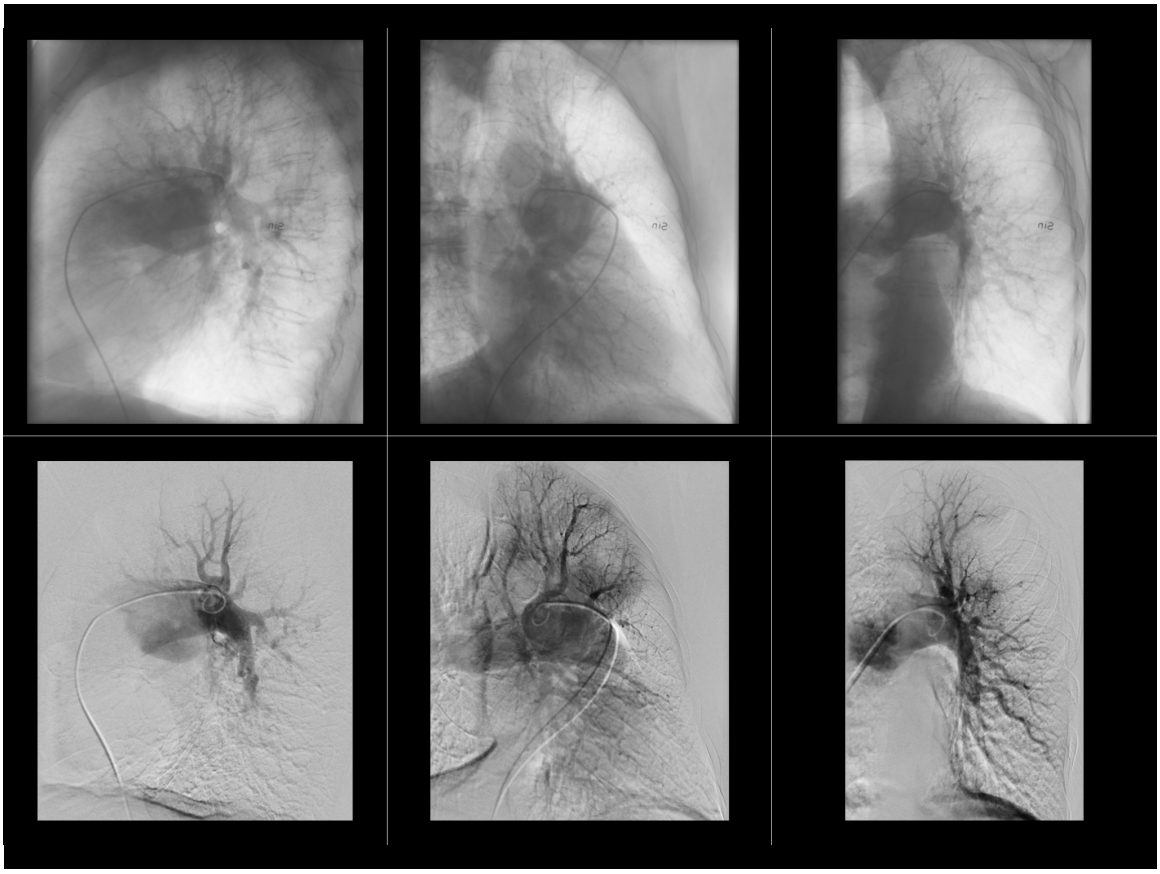

Figure 1. *Example of images from a pulmonary angiography. The catheter used can be seen in the pulmonary artery.*

2.3.4 Ventilation perfusion scintigraphy

Ventilation perfusion scintigraphy (V/Q scan) was first introduced in the mid 1960s. In the 1980s the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study compared the results for V/Q scans with conventional pulmonary angiography. It showed that V/Q scans have a high sensitivity (98%), but low specificity (10%) (43). However, it was non-invasive unlike pulmonary angiography and in the following years scintigraphy became the first line diagnostic test in cases of suspected APE due to its safety.

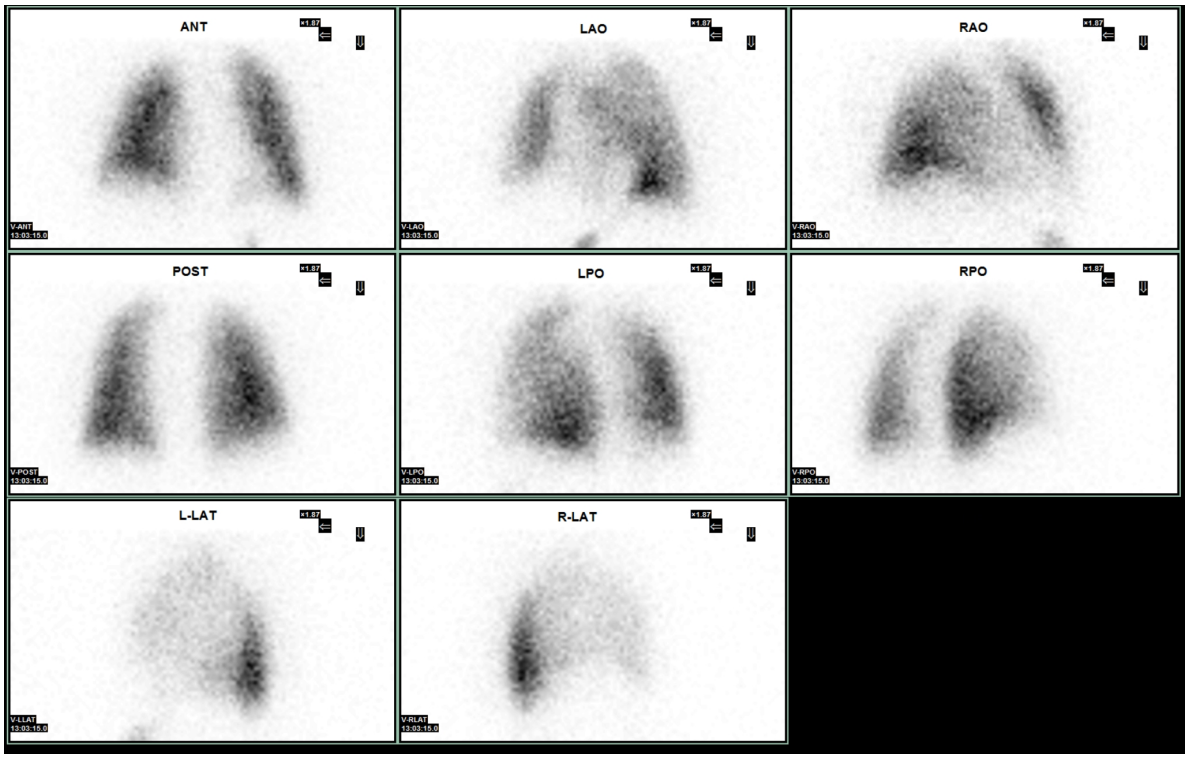

Figure 2. *Example of a VQ-scan.*

In V/Q scans radioisotopes are administered and imaged by a gamma camera. Perfusion scintigraphy is performed with ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA), which is injected into a peripheral vein. The ^{99m}Tc-MAA is distributed in the lungs according to the regional lung perfusion and trapped in the pre-capillary arteries (particle size 15-100 μm) (44). The perfusion scan is often combined with a ventilation scintigraphy, where ^{99m}Tc-aerosols commonly are inhaled. However, there are a number of options and inert gases such as ^{81m}Kr and ^{133}Xe can also be used (45). The combination of ventilation and perfusion increases the specificity and yields additional information about other conditions (46). Perfusion defects with normal ventilation (V/Q mismatch) may indicate APE or CTEPH. Characteristic perfusion defects are wedge shaped lobar, segmental or subsegmental with a distribution according to vascular anatomy. However, similar findings can be seen in several

other conditions. To make things even more complicated APE can manifest as a matched defect in cases of pulmonary infarction.

Apart from the low specificity, limitations for V/Q scanning include the probabilistic classification, the number of indeterminate exams, interobserver variability, the relatively long examination time and inability to detect differential diagnoses (36). In addition, the availability is usually limited after office hours.

At present CTPA has replaced V/Q scans as the first line diagnostic method in patients with suspected APE. However, for patients with contraindications to CTPA or during pregnancy, it is still frequently used. Regarding CTEPH the V/Q scan is still recommended as a screening test in international guidelines since it can safely rule out CTEPH in PH patients (10).

2.3.5 Computed tomography pulmonary angiography

The CT was first introduced in the early 1970s and APE was first reported in 1978 as an incidental finding (36). But it was not until 1992 and a publication by Remy-Jardin that spiral CTPA emerged as a potential modality to detect APE (47). First-generation CT scans with single detector rows had a sensitivity of 53% and 91% specificity for APE (9, 38). The technical development, including the introduction of multidetector row CT, has improved image quality as well as acquisition time. In multidetector CT the sensitivity varies between 83–100% and the specificity between 89–97% (38). One of the studies that established multidetector CTPA as a diagnostic option was the PIOPED II trial: A prospective multicentre study on 824 patients during 2001–2003 (48). It found a sensitivity of 83% and specificity of 96% for APE. Except for the high diagnostic accuracy CT also offers alternative causes of symptoms, unlike for instance V/Q scans. The clinical validity of a negative CTPA scan is similar to that of conventional pulmonary angiography (38). In addition CTPA is widely available and has a short acquisition time (4–5 seconds in a 64 row scanner).

Imaging is an essential part of the diagnostic algorithm in CTEPH as well, and CT is mentioned as a diagnostic option in the 2015 ESC/ERS guidelines on pulmonary hypertension (10). Several studies have established that CT has a high specificity (93-100%) for CTEPH (49-54), but the sensitivity remains under debate. A study on 55 CTEPH patients by Bergin et al from 1997 (49) showed promising results regarding both sensitivity and specificity and two more recent studies on 24 and 27 CTEPH patients respectively showed a sensitivity of 98–100% for lobar arteries and 94–100% on the segmental level (51, 55). There are two more recent studies on 114 and 132 consecutive patients (51 and 78 patients with confirmed CTEPH diagnosis respectively) that showed sensitivities of 92–94% (52, 54). Still, the largest and most frequently cited study is from 2007 showed conflicting results with a sensitivity of only 51% for CT (50), this will be further discussed in the discussion section.

During CT examinations, consecutive x-ray projections from different angles of the body produce cross-sectional images by computer processing. For visualisation of potential emboli iodinated contrast media must be administered and the contrast bolus must be caught while within the pulmonary arteries (a time span of approximately 10 seconds) (7).

Limitations regarding CTPA include the exposure to ionizing radiation and the administration of contrast media. Impaired renal function is a contraindication for CTPA and contrast allergy may also be a problem. Regarding pregnant patients it has been debated whether CTPA or V/Q scan is most appropriate (56) but according to the 2019 ESC guidelines the choice of imaging should be determined by local expertise and resources (15).

The diagnostic signs of APE on CTPA are: 1) Arterial occlusion, the diameter of the occluded artery is often enlarged compared to surrounding vessels, fig 6. 2) Partial filling defect surrounded by contrast material, also known as the ’polo mint’ or ’railway track’ sign. 3) The partial filling defect may sometimes be eccentric, but in this case it should form acute angles with the vessel wall. Infarctions can be seen as wedge shaped infiltrates in the peripheral lung regions, but this finding has a low specificity, fig 5. In addition, signs of acute right ventricular failure should be described, as these patients may be at risk of circulatory collapse. CT findings of this include right ventricular dilatation, deviation of interventricular septum to the left and reflux of contrast material into the hepatic veins. (57)

In cases of CTEPH, there are several radiological features to keep in mind. These may be divided into direct pulmonary arterial findings, signs of PH and parenchymal signs. Among pulmonary arterial findings there are: 1) Complete occlusion, sometimes causing a so-called ‘pouch defect’. Occluded vessels, particularly on the segmental and subsegmental level show reduced vessel diameter 2) Partial filling defects that are usually eccentric with obtuse angles towards the vessel wall. 3) Signs of recanalization such as bands and webs, depicted as thin lines surrounded by contrast material. (8, 57). 4) Calcified thrombus. Signs of PH include: 1) Increased diameter of the main pulmonary artery (MPA) >29 mm in men and >27 mm in women. 2) Increased MPA-ascending aorta (AA) ratio >1:1, since the AA widens with age this sign is most useful in patients <50 years. 3) Tortuous vessels. 4) Increased systemic collateral arteries, a non-specific sign, which however appears to be more common among CTEPH patients than other groups of PH patients. 5) Right heart disease is including right ventricular enlargement (a ratio of the right ventricle compared to the left >1:1), right ventricular hypertrophy (RVH) with a myocardial thickness >4 mm and interventricular septum deviating to the left. In severe cases there may also be pericardial thickening or a small pericardial effusion. Regarding parenchymal signs there are: 1) Mosaic attenuation, a pattern of increased and decreased attenuation of the lung parenchyma where the low attenuating areas represent hypoperfusion. This sign is considered non-specific, but in patients with PH it is usually related to CTEPH. 2) Scars, following previous infarctions. 3) Infarctions also appear to occur in patients with CTEPH, even without acute components. (8, 57)

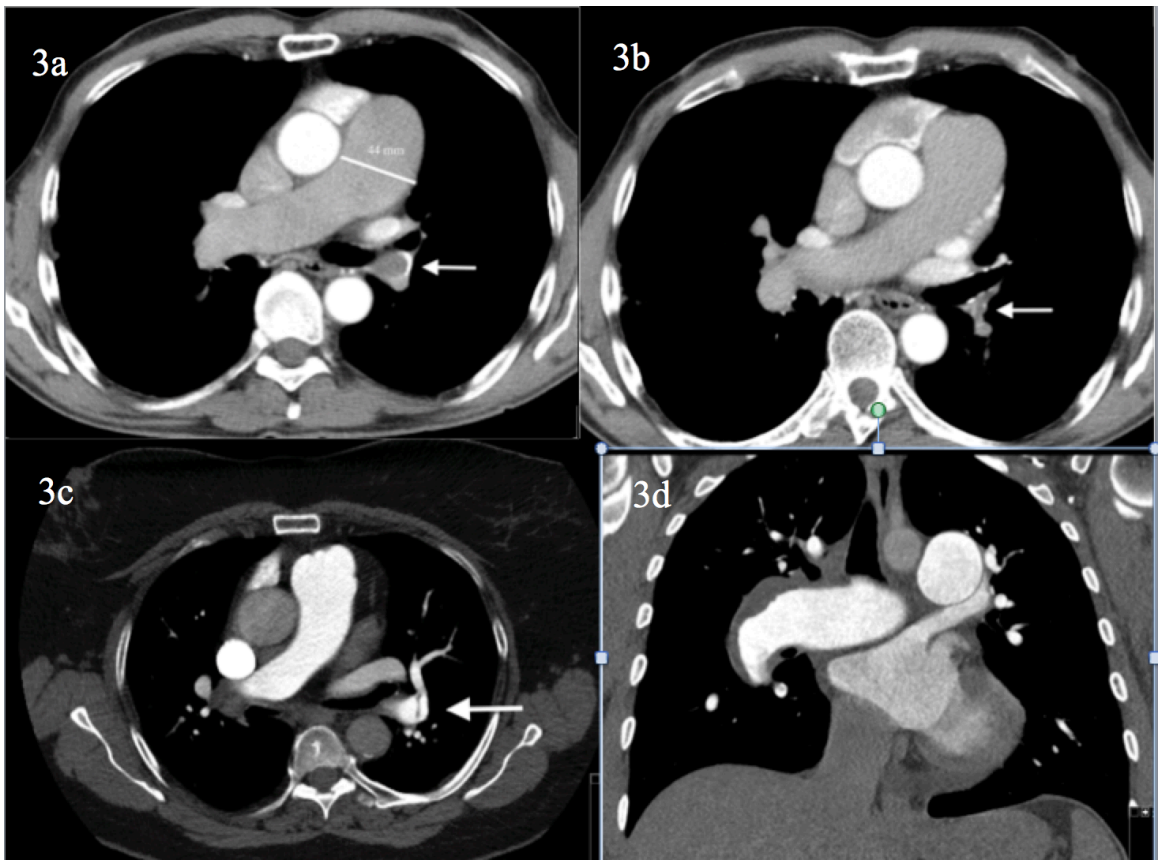

Fig 3. *Vascular signs associated with CTEPH. a) Increased diameter of the MPA (44 mm) and a calcified thrombus in the left lower lobe artery. b) Occlusion with reduced vessel diameter in segmental arteries in the left lower lobe. c) A band in the left lower lobe artery, visualised as a thin line surrounded by contrast. d) Eccentric thrombus in the right pulmonary artery.*

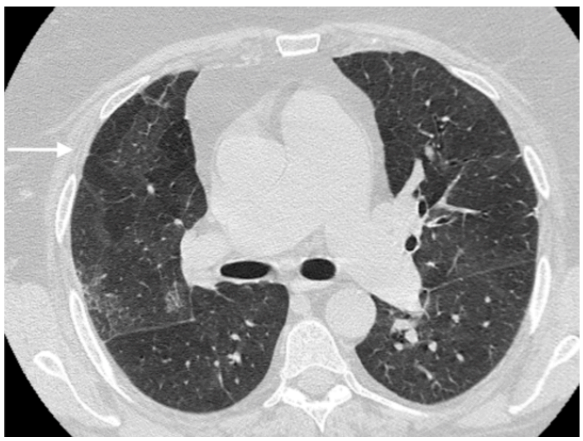

Fig 4. *Mosaic attenuation, seen as areas of different attenuation in the lung parenchyma.*

CTEPH is considered to be frequently missed and underdiagnosed for a number of reasons including lack of knowledge of the condition among radiologists (11, 12) . Obviously, an understanding of the radiological features is required to detect the condition on exams from various imaging modalities.

At present, both the American College of Radiology, the European Society of Cardiology (ESC) and Fleischner Society recommend CTPA as the first line test in patients with suspected APE, while the Fleischner Society even suggests it as the new gold standard (38, 58). According to 2015 ESC/ERS guidelines, CTPA is part of the diagnostic algorithm in patients with suspected CTEPH, but V/Q scan remains the recommended first-line screening option and conventional pulmonary angiography is still recommended for presurgical assessment (10).

2.3.6 Magnetic resonance imaging

The magnetic resonance phenomenon was first discovered in the mid-1940s but it was not until the 1970s that it was used to demonstrate human pathology. Magnetic resonance imaging (MRI) of the lungs was first introduced in the 1980s (59). Among the early limitations in clinical practice were limited spatial resolution, motion artefacts, long acquisition time and in severely ill patients, the lack of MR-compatible monitoring devices (60). Increasing technical development has made MRI less susceptible to these limitations. It has been suggested that MRI could emerge as a diagnostic option regarding APE, particularly in patients not suitable for CTPA (6, 61). Nevertheless, MRI is not fully accepted yet as a diagnostic test in patients with suspected APE due to limited sensitivity (7, 61).

In MRI radio waves are applied to a magnetic field to produce sectional images of the body. Technically there are a number of different ways to visualise embolism in the pulmonary arteries. Gadolinum enhanced magnetic resonance angiography (Gd-MRA) is the most frequently studied method. It is similar to CTPA in the respect that contrast media is administered, however, with the longer acquisition time in MRA (15-20 seconds) it is more difficult to time the bolus so that all pulmonary arteries are well opacified (7). Unenhanced MRI sequences are also used, such as steady-state free precession (SSFP) where movement of the blood flow creates high signal intensity in the arteries and emboli can be detected as signal voids. MRI perfusion can be used to detect perfusion defects and has been described to have high agreement with scintigraphic methods (62).

The findings in APE on MRI are similar to those on CTPA, since both exams visualise the same morphological information. Thus, occlusion and partial filling defects surrounded by contrast material are the main findings. Wedge-shaped perfusion defects and infarction can also be seen. The main difference in interpreting MRI compared to CTPA is the artefacts. (60, 63)

In CTEPH the expected MRI findings are also similar to those seen on CTPA. An early study by Ley et al from 2003 showed that MRI is equal to CTPA on segmental level, but CTPA was superior on the subsegmental level and for evaluating intraluminal webs and thrombotic wall thickening (55). Technical advances in MRI have likely improved the diagnostic capability since then, but there are no recent studies comparing MRI and CTPA in CTEPH and the usefulness of MRI in diagnosing CTEPH is unestablished (63).

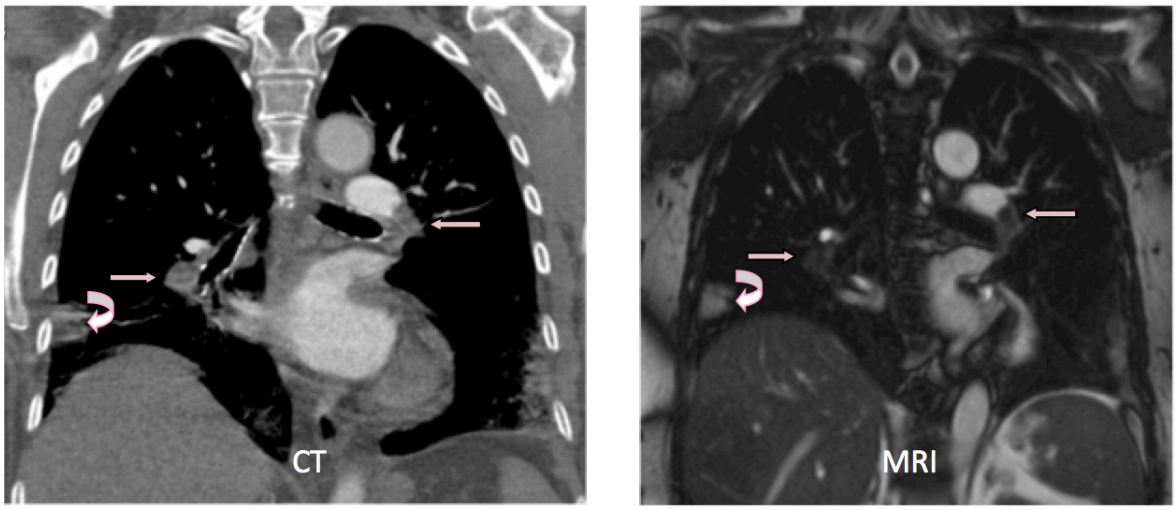

Fig 5. *Examples of images from CTPA (left) and MRI (right) in a 83-year old patient with APE. Emboli can be seen in the right lower lobe artery and in the left intermediate artery (arrows), in addition an infarction can be seen in the right lung (bent arrow.)*

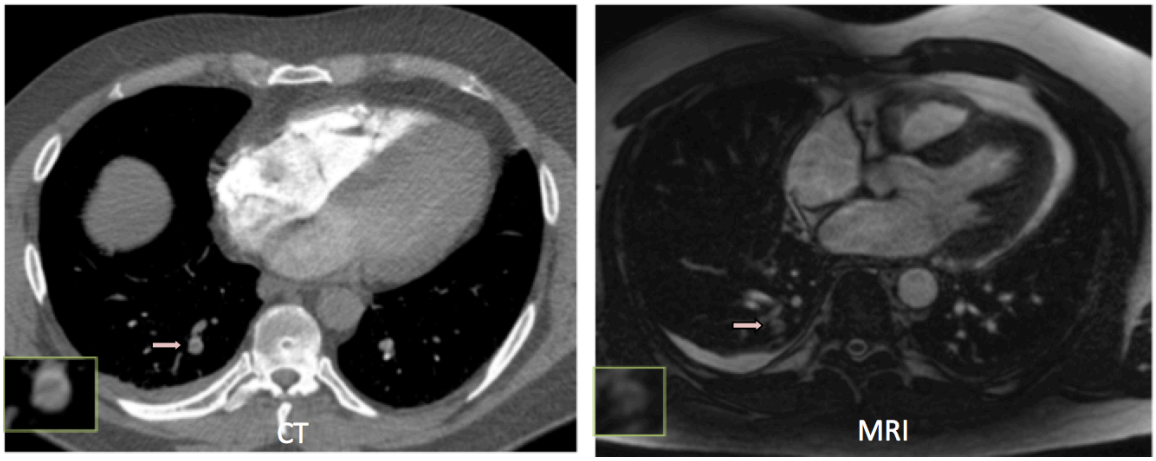

Fig 6. *Examples of images from CTPA (left) and MRI (right) in a 52-year old patient with an isolated subsegmental embolus in the right lower lobe (arrow). Note that the affected artery is enlarged compared to surrounding arteries. A small pleural effusion can be seen on the right side. In the right lower corner magnifications illustrate the 'polo mint sign'*

There are two recent meta-analyses on the topic of MRI and APE. In 2015 Zhou et al published information based on 24 studies, 15 of which were patient based and 9 vessel based, from 1993–2013. The number of technically inadequate investigations was 19%, which is three times higher than in CTPA. When the technically inadequate investigations were excluded, MRI had a sensitivity of 78% and a specificity of 97% on a patient based level, which is similar to the diagnostic performance of CTPA in the PIOPED II study. However, 10 of 15 studies had a small sample size (<89 subjects) and 8 of 15 studies had a considerably higher prevalence of APE than expected, making selection bias likely; Zhou

finds it possible that these aspects might have made the results favourable for MRI. On a vessel-based level, Zhou found a high sensitivity for MRI in lobar and segmental vessels (91-94%), but a low sensitivity (55%) on the subsegmental level. (6)

The second meta-analysis was performed by Li et al in 2016 though it only assessed Gd-MRA in five studies, all of which were also included in Zhou's study. The conclusion was that Gd-MRA can be used to detect APE, but should not be used as a stand-alone test to exclude APE due to its limited sensitivity. (61)

The most important studies in the field of MRI in the detection of APE are PIOPED III- and the IRM-EP studies, both of these were included in the meta-analyses by Zhou and Li (64, 65). The PIOPED III study, a prospective multicenter study performed 2006–2008 on 371 patients, analysed the diagnostic accuracy of Gd-MRA alone and combined with thigh venography in APE. The number of technically inadequate investigations was high (25%) ranging from 11% to 52% at different centers. The most common causes of inadequate exams were poor arterial opacification (67%) and motion artefacts (36%), but also MRI specific artefacts such as wraparound (4%) and parallel imaging artefacts (2%) occurred. Among the technically adequate investigations the sensitivity was 78% and specificity 99% on a patient based level. On a vascular level it was noted that the sensitivity decreased with vessel size, with a sensitivity of 79% in main or lobar arteries, 50 in segmental arteries and 0% in subsegmental arteries. The conclusion of PIOPED III was that Gd-MRA only should be considered at experienced centers and only in patients with contraindications for the standard diagnostic examinations. (64)

The IRM-EP study from 2012–2013 by Revel et al was also a prospective study, performed at a French University Hospital during 2007-2009. The purpose of the study was to evaluate new MR-sequences including unenhanced and perfusion sequences in addition to MRA and to investigate if MRI could be used as a diagnostic test in APE-patients. The proportion of technically inadequate exams was 30%. Combining all MR sequences in the assessment for the technically adequate exams the overall sensitivity was 79–85% and the sensitivity was 99–100%. There was a high sensitivity (98–100%) in proximal APE, but the sensitivity decreased with vessel size (68–91% on segmental level and 21–33 on subsegmental level). MRA exams had the highest sensitivity. Perfusion sequences had a slightly higher sensitivity than unenhanced exams, but the unenhanced exams showed a higher specificity and interreader agreement. (62, 65)

MRI has the potential to be well suited for CTEPH patients as it offers evaluation of right ventricular function in addition to pulmonary arterial findings and alternative causes of PH (46). The number of studies on the topic is scarce. MRI perfusion has demonstrated similar sensitivity compared to V/Q scans (52) and MRI shows a high sensitivity for obstruction in central arteries (66). Nevertheless, CT has a higher sensitivity on the subsegmental level, in the detection of intraluminal webs and thrombotic wall thickening (55). In summary, the utility of MRI for diagnosing CTEPH has not been established as yet (63).

At present, according to the 2019 ESC guidelines, MRI has shown promising results for APE but is not ready for clinical practice (15). The reasons for this decision are the low sensitivity, the high proportion of technically inadequate exams and the low availability in the emergency setting. However, it should be mentioned that there have been advances in the MRI technology, including spatial resolution, since the PIOPED III and IRM-EP studies. It has also been argued that MRI may be useful in CTEPH patients as it enables both assessment of pulmonary arteries and right ventricular function but the number of studies is limited, and the method must be validated. (9, 46, 63). The awareness of thoracic findings on MRI has increased in recent years and there are studies encouraging radiologists to look for thoracic findings such as PE on abdominal MRIs (67).

2.4 PATIENTS SUITABLE FOR MRI

For the depiction of emboli in the pulmonary arteries on CT, intravenous administration of iodinated contrast media is required. In patients with severe renal impairment, iodinated contrast media is contraindicated since it may cause contrast-induced nephropathy. Patients allergic to iodinated contrast media may also cause a problem, but allergic reactions can often be avoided by the use of premedication. In the PIOPED II study, 19% of patients with suspected APE had abnormal creatinine levels and 4% were allergic to contrast agents (48). It has been reported that 12% of patients with elevated creatinine levels and suspected APE may develop contrast-induced nephropathy following CTPA (68).

Pregnant patients have an increased risk of APE due to hormonal changes and APE is the leading cause of pregnancy-related mortality in developed countries (56). It has been debated whether CTPA or V/Q scan is most appropriate (56). The diagnostic yield for both examinations is similar (69), since the results for V/Q scan is better in young patients without any pulmonary disease, while the number of inconclusive CT scans is higher due to difficulties in catching the contrast bolus with the increased blood volume during pregnancy. Fetal radiation doses are also similar for V/Q scans and CT. It used to be argued that the radiation to the maternal breast among pregnant women constituted a problem (70), but with ongoing technical development this is no longer the case (15).

To summarize, patients with renal impairment and pregnant patients are among the patient groups that could benefit the most from a contrast- and radiation-free imaging modality.

2.5 PEDAGOGICAL ASPECTS

During radiology residency junior physicians are educated within the field of radiology to become attending physicians. A high standard of quality in the residency program is important to achieve well-qualified radiologists. In fact, there is an established relationship between clinical learning environment and patient safety (71). Furthermore, with the rapid technical development within the field of radiology it must be argued that continuous learning throughout the career is required. However, a problem with radiology education is the scarcity of measurable data with regard to the learning process during residency (14).

In the field of medical education, there is an ongoing transition from the traditional time-based models to outcome-based learning models, focusing more on the final capabilities (72, 73). American recommendations for Medical Education Reform 2010 urged updated pedagogy, including learning in context, mentorship, extensive feedback and time for personal reflection (72).

Deliberate practice has proven useful as an educational strategy in various fields of education (74). In this training method the learner is 1) given a task exceeding current level of skills, 2) motivated to practice and improve, 3) provided with instant effective feedback, and 4) encouraged to reflect on the learning experience (75). In addition, the learner should perform the same or similar tasks repeatedly. When the method is followed, practice should improve both accuracy and speed of performance on cognitive, perceptual and motor skills (76).

In medical education, deliberate practice has been suggested particularly in radiology training, electrocardiogram interpretation and surgery stimulation (74, 77). Visualizing the effect of deliberate practice by plotting learning curves with the performance against time spent learning, it is possible to define at which levels education is most efficient and how much training is required for a certain level of competence (74, 78). Accordingly, this is the method used in *Study II*. Not only is it important for radiology educators to understand how people learn, it has also been argued that emphasis should rather focus on learner progress rather than the learner's absolute level of knowledge (79). Thus, a thorough understanding of learning curve effects is important to produce an ideal learning environment (79).

Studies on learning curve effects in radiology usually focus on identifying a specific diagnosis or anatomical structure on certain examinations (14, 77, 78, 80). Most studies include either relatively few reviewers or training examinations. In addition, different outcome measures are used to assess improvements in diagnostic ability over time, including sensitivity/specificity, ROC-analysis and interreader agreement, making direct comparison among studies more difficult. There appears to be a general agreement that the amount of training is an important factor to achieve a high diagnostic accuracy (77, 78, 81), while the effects of previous radiologic experience on the ability to learn new radiologic methods have not been established (14, 80). A few studies have shown a positive effect on the review time, but not on diagnostic accuracy (78, 80). It could be that review time is reduced before improvement in diagnostic accuracy is seen. Except for *Study II* there is one other study

where the learners' previous knowledge is scarce and in both these, a learning curve effect regarding accuracy is seen (14).

In studies on MRI in the detection of APE, primarily senior, experienced radiologists have reviewed the exams (65, 82-85). However, in a clinical setting residents are commonly the primary reviewers (81). When introducing a new method, knowledge of the learning curves is of particular interest. In addition, the knowledge could be of general interest to improve the understanding of how residents learn.

3 AIMS OF THESIS

General aim

The general aim of the thesis was to investigate emerging imaging modalities in the diagnosis of APE and CTEPH and the knowledge of theses among radiologists.

3.1 STUDY I

"Detection of pulmonary embolism using repeated MRI acquisitions without respiratory gating: A preliminary study."

The aim of the study was to determine the sensitivity and specificity of repeated acquisitions of unenhanced MRI in the detection of APE.

Our hypothesis was that unenhanced MRI with repeated acquisitions could be used as a diagnostic test in patients with suspected APE.

3.2 STUDY II

"How to train radiology residents to diagnose pulmonary embolism using a dedicated MRI protocol."

The aim of the study was to evaluate if residents in radiology can be trained to review MRI regarding APE and to examine the learning curve effects.

Our hypothesis was that it is possible for residents to independently learn how to interpret MRI regarding APE within a self-directed training program.

3.3 STUDY III

"Sensitivity of computed tomography pulmonary angiography for diagnosing chronic thromboembolic pulmonary hypertension."

The aim of the study was to investigate the sensitivity of CTPA in patients with CTEPH.

Our hypothesis was that CTPA has a high sensitivity for CTEPH.

3.4 STUDY IV

Do radiologists detect chronic thromboembolic disease on computed tomography?

The aim of the study was to evaluate the extent of misdiagnosis of CTEPH on CT.

Our hypothesis was that general radiologists frequently miss CTPH findings on CT.

4 METHODOLOGICAL CONSIDERATIONS

4.1 STUDY I

"Detection of pulmonary embolism using repeated MRI acquisitions without respiratory gating: A preliminary study."

Study I was a prospective study approved by the regional ethical committee in Stockholm, Sweden (Dnr 2011/1592-31/1 and 2013/1984-32). Written informed consent was obtained from each participant.

4.1.1 Subjects

From February 2012 to January 2014 patients with a clinical suspicion of pulmonary embolism (PE) that had performed a computed tomography pulmonary angiography (CTPA) were given the option to participate in the study. Exclusion criteria were contraindications to MRI and a time span between the CTPA and MRI examinations exceeding 48 hours.

The included patients underwent magnetic resonance imaging (MRI) within 48 hours after the CT exam. Participation in the study did not affect any treatment regimen, thus patients with APE on the CTPA received anticoagulation therapy prior to the MRI exam. One patient, a 51-year old woman, had a MRI incompatible breast implant and was excluded. A group of 33 patients, 23 men and 10 women, average age 48 years, age range 22–87 years, were included in the study.

Due to the time gap between the CT- and MRI exam (average time 22 hours and 39 minutes and time span 4 hours 28 minutes to 47 hours 22 minutes) primarily patients admitted to the hospital agreed to participate. Therefore, the number of patients (two men and two women) without PE was unproportionally low. To compensate for the small number of normal exams, a control group of 37 healthy subjects (nine men and 28 women; average age 48 years, age range 26–66 years) was created. The healthy controls underwent the MRI-exam and an equal number of normal CTPAs from the hospital's patient flow were added.

The high proportion of positive findings (patients with APE on the CTPA) in the patient group should be noted. A positive result of PE should be expected in no more than 10–20% of patients referred for CT (28, 29). Therefore, selection bias must be considered. Only two physicians referred patients to the study, which means that many patients with suspected APE probably were not invited to participate. The time gap between CT and MRI can also explain the selection bias. Patients asked to participate in the study that declined the offer were not registered and this was also a weakness of the methodology.

4.1.2 CT-protocol

The CTPA exams were performed by a 64-section CT scanner, Lightspeed VCT, GE Healthcare, Milwaukee, USA. According to a standardised protocol at the radiology department. For detailed information about CT parameters and contrast administration, please see *Study I*, page 273.

4.1.3 MRI-protocol

The MRI exams were performed by a 1.5 T MRI scanner (Magnetom Aera, Siemens Medical Systems, Erlangen, Germany) using 2D free-breathing steady-state free precession (SSFP) sequences, without any intravenous contrast agent, and respiratory or cardiac gating. Unlike previous studies that often use cardiac and/or respiratory gating, we decided to evaluate a novel method using five repetitive slices in each anatomical position, to compensate for movements caused by respiration. The repetitive slices were sorted by position in image stacks. There were no specific breathing instructions. Total acquisition time was 9:34 min. For MRI parameters please see *Study I*.

4.1.4 Image analysis

All CT- and MRI exams were anonymised and blinded prior to analysis. The patient and control exams were also randomly mixed. The presence of APE was based on vascular signs only, that is complete or partial filling defects. Indirect signs, eg. infarction was not used for the assessment.

A senior radiologist with more than 10 years of experience in thoracic radiology reviewed the CT exams and this reading was considered gold standard.

The MRI exams were reviewed by two radiologists (R1 and R2). Both reviewers had one year's experience in thoracic radiology, but R1 also had some experience in cardiac MRI.

Both the CT- and the MRI reviewers reviewed the exams according to a standardised form where the vascular bed was divided into territories according to a model previously described by Kalb (82). If an embolus was detected, the vessels distal to it were not further evaluated.

4.1.5 Statistical analysis

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated with 95 percent confidence intervals (95% CI) using MedCalc Software (86). GraphPad Software (87) was used calculating Kappa values to determine the interreader agreement between the MRI readers.

4.2 STUDY II

"How to train radiology residents to diagnose pulmonary embolism using a dedicated MRI protocol."

Study II was approved by the regional ethical committee in Stockholm, Sweden (Dnr 2016/2392-32/1). Informed consent was obtained from each resident participating.

4.2.1 Subjects

The MRI- and CT exams from *Study I* were used to create a self-directed training program.

Four radiology residents (R1–R4) performed the training program independently. Resident R1 had 3,5 years of experience of radiology and three weeks of prior MRI. Resident R2 had three years training in radiology and three weeks of general MRI. R3 had 4,5 years practice in radiology and three months of MRI. R4 had 2,5 years radiology training and two weeks of MRI. All the residents were accustomed to diagnose APE on CTPA, but they all had limited MRI practice.

4.2.2 Image analysis

The principles of image analysis and the report form were the same as in *Study I*, except that the review time for each MRI exam also was registered.

4.2.3 Training program

The training program constituted ten training sessions with seven MRI exams in each. Following each completed session, the participating resident handed in the report form and retrieved the reference standard including access to corresponding CT exams for comparison with their own reading. The reference standard was based on a consensus reading by the two MRI reviewers from *Study 1*. After comparing their own reading with the reference, the resident was allowed to continue on with the next session. Residents R1 and R2 performed the training program in the chronological order starting with session one, while R3 and R4 took the training program in the reversed order starting with session ten. In this study we only examined one training program and it could be interesting in the future to compare different training programs and possibly add a group of residents that assessed the same investigations without receiving any feedback as a baseline.

4.2.4 Statistical analysis

Descriptive statistics including mean and range regarding review time for each resident was determined and p-values and r-values were calculated using Excel Data Analysis Tool Pak (Microsoft Office, Redmond, WA, USA).

Sensitivity, specificity, PPV and NPV was calculated for each resident compared to the reference standard as well as kappa values. Due to the small size of each training session the sessions were paired in chronological order; that is statistics were calculated on 14 consecutive cases. The statistical problem with the small size training sessions could probably have been foreseen, but on the other hand we found it desirable with frequent evaluation of the residents' reviews.

4.3 STUDY III

"Sensitivity of computed tomography pulmonary angiography for diagnosing chronic thromboembolic pulmonary hypertension."

Study III and *IV* were retrospective case-control studies approved by the regional ethical committee in Stockholm, Sweden (Dnr 2017/625-31/1). In agreement with the ethical permit informed consent was waived.

4.3.1 Subjects

4.3.1.1 Cases

All patients referred for pre-surgical assessment for pulmonary endarterectomy during 2011–2016 (n=48). Patients without a prior CTPA (n=13) were excluded. The remaining 35 CTPA exams were performed at 23 different hospitals, so differences in CT-protocols could be expected. These differences and quality are one of the weaknesses of the study. Another weakness is that patients referred for surgery is a selected group, and they are likely to have relatively proximal disease. Since proximal disease will be easier to detect on CT, it is possible that the sensitivity was falsely high. Finally, the study population was relatively small and so are many of the studies in the field of CTEPH as it is considered a rare condition.

4.3.1.2 Controls

Patients examined with CTPA due to suspected APE. Each control was matched according to age (+/- 5 years), gender and date of the CTPA (+/- 2 years).

4.3.2 Image analysis

The CTPAs from cases and controls were anonymised and mixed randomly prior to image analysis. Two radiologists evaluated all the CTPAs according to a standardised form. In case of disagreement a consensus reading was performed.

4.3.3 Statistical analysis

Sensitivity, specificity, PPV and NPV with 95% CI were calculated. Calculations were made on diagnostic level and for each individual sign of CTEPH. In cases of disagreement a consensus reading was made.

4.4 STUDY IV

"Do radiologists detect chronic thromboembolic disease on computed tomography?"

For ethical permit, see *Study III*.

4.4.1 Cases and controls

The cases and controls were the same as in *Study III*.

4.4.2 Assessment of original reports

The original CT reports were retrieved from the picture archiving and communications system (PACS). The reports were evaluated according to a standardised form and the results were compared to a consensus reading by two thoracic radiologists. Except for radiological findings it was noted if the CT exam was performed in a university hospital or a non-specialist centre.

4.4.3 Statistical analysis

Sensitivity with 95% CI was calculated on a diagnostic level and for each radiological finding associated with CTEPH. We also made a comparison between university hospitals with non-university hospitals.

5 RESULTS

5.1 STUDY I

"Detection of pulmonary embolism using repeated MRI acquisitions without respiratory gating: A preliminary study."

All the CT and MRI exams were of diagnostic quality. CTPA detected 29 patients with APE, which was proximal in 21 patients and segmental or subsegmental in 8 patients. On MRI, the reviewers identified 26 and 27 patients with APE respectively. The sensitivity compared with CTPA was 93% (95% CI 76-99%) and 90% (95% CI 73-98%) for the readers respectively. Specificity was 100% (95% CI 91 - 100%) for both reviewers. PPV was 100% (95% CI 87-100%) for both. NPV was 95% (95% CI 84-99%) and 93% (95% CI 81-99%) respectively. The interreader agreement between the MRI reviewers was almost perfect with a kappa value of 0.97 (95% CI 0.91-1.00). The two patients with false negative MRI exams underwent a consensus reading. It was noted that both were cases of isolated subsegmental emboli. One of them was seen by one of the reviewers, but in the other patient the embolus could not be seen even after comparison with the CTPA.

5.2 STUDY II

"How to train radiology residents to diagnose pulmonary embolism using a dedicated MRI protocol."

5.2.1 Agreement with reference standard

Two residents (R3 and R4) showed an evident improvement in kappa values compared to the reference standard during the training program. Also R1 and R2 showed an improvement over time, but this finding was weaker than for R3 and R4. All residents showed very good or perfect inter-reader agreement after seven session or approximately 50 MRI cases.

The improvement during the training program was mainly due to a reduction of false positive findings, but there was also a small decrease in false negative assessments. Session six stood out as more difficult than the other sessions for all residents except for R3. Thus a potential weakness of our model was different levels of difficulty in the different sessions.

5.2.2 Review time

The mean review time among the residents throughout the training program varied from 03:04 minutes to 06:06 minutes, with a mean review time for all residents of 03:56 (00:13-

12:00). However, the pattern over time was similar for three out of four residents with a steep decrease in time during the first three or four training sessions followed by a more gradual decrease. One of the residents (R3) showed a gradual decrease in reading time throughout the training program. The decrease in review time was statistically significant (p = 0.0002).

5.3 STUDY III

"Sensitivity of computed tomography pulmonary angiography for diagnosing chronic thromboembolic pulmonary hypertension."

The consensus reading yielded a sensitivity of 100% for CTEPH on a diagnostic level on CTPA. The individual sensitivities for each reviewer were 89% (95% CI 73–97%) and 94% (81–99%). The specificity for each reviewer was 91% (95% CI 81–99%) and 94% (95% CI 81–99%) and in the consensus reading the specificity was 91%. The inter-reader agreement was kappa 0.77 (95% CI 0.66–0.92).

Seven vascular signs associated with CTEPH were assessed and the sensitivity for these ranged from 6%–91%. The specificity ranged from 74–100%.

5.4 STUDY IV

"Do radiologists detect chronic thromboembolic disease on computed tomography?"

The consensus reading from *Study III* with a sensitivity of 100% was used as the reference standard for comparison with the original CT reports. The overall sensitivity on diagnostic level in the original reports was 26% (95% CI 13–43). The overall sensitivity among university hospitals was 63% (95% CI 25–92) and among non-specialist centres 15% (95% CI 4-34%). Pulmonary arterial findings without mentioning of any sign of PH had a sensitivity of 63% (95% CI 45-79%), isolated signs of pulmonary hypertension 53% (95% CI 35-71%) and mosaic attenuation 6% (95% CI 1-20%) in the original reports.

6 DISCUSSION AND CONCLUSIONS

6.1 MAJOR FINDINGS

The major findings from the studies included in this thesis are: 1) Unenhanced MRI using repetitive acquisitions instead of gating has a high sensitivity and specificity for APE. The method also yields a high proportion of technically adequate investigations. 2) By using a self-directed training program, residents can learn how to interpret dedicated MRI-exams regarding PE. 3) CTPA shows a high sensitivity and specificity regarding CTEPH when reviewed by expert radiologists. 4) There is a limited knowledge among Swedish general radiologists regarding CTEPH-findings on CT, leading to a falsely low sensitivity.

6.2 DISCUSSION

Combined MRI protocols have the best diagnostic performance (6), but they tend to comprise gadolinium-enhanced series. In 2006 Grobner et al published a small set of data on a relationship between gadolinium contrast administration and nephrogenic systemic fibrosis (NSF) (88). In pregnancy, a number of complications including neonatal death has been described following exposure to gadolinium contrast, while unenhanced MRI has shown no negative effects regardless trimester in a recent study on 1.5 million pregnancies (89). Given that patients with impaired renal function and pregnant patients are among the patient groups that could benefit the most from MRI, gadolinium-enhanced protocols are less interesting from a practical point of view.

With the introduction of multidetector CT, the number of detected isolated subsegmental APE has increased from 5% to 9% (9). The clinical relevance of isolated subsegmental emboli has been questioned, not at least considering the risks associated with anticoagulation therapy (42). There are also concerns that CT might be overdiagnosing distal emboli, since conventional angiographic studies have shown a lower prevalence of 4–6% subsegmental emboli (38). According to the 2016 CHEST guidelines, subsegmental APE without any proximal DVT clinical surveillance is recommended instead of anticoagulation when the risk of recurring VTE is low (90). In fact, withholding anticoagulation in isolated subsegmental APE was suggested already in 2007 according to a statement by Fleischner Society, however, the statement also recommended anticoagulation in patients with inadequate cardiopulmonary reserve (38). To summarise, the diagnostic ability for subsegmental APE regardless of imaging modality is difficult to assess and the clinical significance of the low sensitivity for MRI on the subsegmental level is unknown.

It is known that CT has a high specificity for CTEPH, but the sensitivity is still questioned. A few small studies (on 24, 27 and 55 patients each) found a high sensitivity for CT (49, 51, 53). However, the sensitivity on the subsegmental level has not been presented in these studies, which is also a weakness since the sensitivity will be lower in more distal disease. There is also a methodological problem, as these studies only included patients with CTEPH

and no controls, which is likely to cause information bias. The most important study in the field is still the study by Tunariu et al from 2007, which is frequently cited as an argument against CT utilization in the diagnostic work up of CTEPH patients. However, the cautious reader will notice that the CT performance was solely based on the original reports. Reports done by radiologists with varying levels of seniority. Thus, the Tunariu study is more likely to reflect the knowledge of CTEPH-findings on CT among the radiologists at that hospital and time than the actual sensitivity. There have also been notable technical improvements in CT since 2000-2005 when the material was collected.

In *Study III* we found a high sensitivity for CT in CTEPH patients when reviewed by an expert reader. The results are similar to those by Bergin et al, Reichelt et al and Ley et al (49, 51, 53) although we only assessed the sensitivity on a patient based level and not on a vessel based level. It should be mentioned that our study population included patients referred for surgery probably left out patients with only distal disease and this might have given a higher sensitivity than in an unselected material. However, the assessment on the subsegmental level shows a low degree of inter-reader agreement regardless of imaging modality (36), (37, 42).

With the increasing utilisation of CT many patients with unexplained dyspnea, such as CTEPH patients, can be expected to have performed a CT. Unfortunately, it has been suggested that radiologists might have a tendency to overlook signs of CTEPH on CT unless specifically asked for. However, there have not been any previous studies on the topic. *Study IV* on the knowledge among Swedish radiologists showed a low sensitivity (26%), with the best results among CT exams reviewed at university hospitals (63%). The result among university hospital radiologists was similar to the Tunariu study (50).

6.3 STRENGTHS

One of the problems using MRI to diagnose APE has been the high number of technically inadequate investigations. The main reasons have been poor arterial opacification and motion artefacts (Zhou). In *Study I* we introduced a method where gating was replaced by repetitive series and among the 70 examined patients there were no technically inadequate exams.

Most previous studies on the sensitivity of CTPA in CTEPH patients have only had patients with confirmed or suspected CTEPH, which is a likely cause of information bias. We decided to perform a case control study instead, which improves the internal validity.

6.4 LIMITATIONS

As mentioned above, the sensitivity and specificity for APE using our MRI protocol was high. However, selection bias may have affected the results in a way favouring a high sensitivity. The proportion of patients with a positive finding of APE was by far exceeding what is seen in clinical practice and there was also a large proportion of proximal APE (21 of

29 patients had central or lobar APE). In addition, the study size was a bit too small, particularly affecting the confidence intervals regarding sensitivity.

The time gap between the CT and MRI is also a limitation. Most studies require less than 36–72 hours between the CT, which is performed first, and the following MRI. This is likely to be a result of the limited availability of MRI in emergency settings. Since the patients receive anticoagulant treatment in cases of confirmed APE on the CT exam or even before the CT exam, small emboli may have resolved by the time of MRI.

In the second study there were only four residents evaluated, but the results from taking the training program were consistent. Still it could have been useful to compare the training program used to other teaching methods. The size of the training sessions should be addressed since each session was too small for individual statistical analysis. However, it was relevant for the residents to receive frequent feedback on their performance.

Regarding the CTEPH studies we decided to include patients referred for the potentially curative surgical procedure PEA. This may cause a certain selection bias, since the patients referred probably will have more proximal disease, which is more easily detected on CT. These patients may also be younger and in a better medical condition, so that they will be able to undergo major surgery. However, this may be the group of CTEPH patients that is most important to detect early, while they are still fit for surgery.

The total number of CTEPH patients is also relatively small, reflecting that it is a rare condition in the general population. This is probably the reason that several other studies in the field also are small. Resulting in broader confidence intervals than desired regarding sensitivity. Regardless of the methodological limitations there is a notable difference between our expert reader and the original reports, indicating that CT actually has a high sensitivity for CTEPH but is frequently missed by general radiologists.

In *Study IV* on knowledge of CTEPH findings among radiologists, the CT exams were all reported in one country. It is likely that signs of CTEPH are missed on CT in other countries as well, but this should be confirmed.

6.5 CONCLUSIONS

In conclusion, we have found a high sensitivity and specificity for APE and a low proportion of technically inadequate investigations using unenhanced MRI with repetitive acquisitions. In addition, we have shown that residents can learn to interpret such MRI exams independently using a self-directed training program. Regarding CTEPH, we have found a high sensitivity and specificity for CTPA exams when reviewed by an expert radiologist, but a limited knowledge among Swedish radiologists in general. Therefore, we suggest that previous CT exams in patients with suspected CTEPH should be reassessed in a specialist centre. A summary of the main conclusions of the thesis is provided in table 2.

Table 2. Main conclusions

- Unenhanced MRI with repetitive series has a high sensitivity and specificity for APE (**Study I**).
- Unenhanced MRI with repetitive series shows a high proportion techically adequate investigations (**Study I**).
- Residents can learn to interpret a dedicated MRI protocol to detect APE using a self-directed training program (**Study II**).
- CT has a high sensitivity for CTEPH when assessed by an expert reader (**Study III**).
- The knowledge of CTEPH findings on CT among general radiologists is poor, leading to a falsely low sensitivity (**Study IV**).

Table 2. *A summary of the main findings of the studies included in this thesis.*

7 FUTURE PERSPECTIVES

In patients with suspected APE that have contraindications to CTPA, MRI has been proposed as a diagnostic option for several years. In the 2019 ESC guidelines however, it is not accepted for clinical practice yet (15). The ACR appropriateness criteria from 2017 on the other hand mention pulmonary MRA together with V/Q scan as diagnostic options if CTPA is not available. The total number of studies in the field is still limited and most are of small size, while the two major studies (PIOPED III and IRM-EP) were performed more than 10 years ago. At present there is an ongoing study investigating if the combination of a negative MRA in combination with a normal proximal compression ultrasound can be used to safely rule out APE. Given the technical development it is important with regular updates, since MRI after all might be introduced clinically in the upcoming years. In fact, a study by Schiebler et al made in 2013 used MRA as a first line investigation for APE. In this study 95% of the exams were of diagnostic quality and during a one-year follow up period the NPV was 96% (91), results similar to that of CTPA.

When it comes to the evaluation of MRI in patients with suspected APE the main focus so far has been on MRA. However, this is not an appropriate method for patients with impaired renal function or pregnant patients. Therefore, it would be desirable with a large-scale study on unenhanced MRI in patients in general preferably with no time gap between the CTPA and MRI examinations. At present there is a meta-analysis on MRI in APE patients and a small meta-analysis focused on MRA, when more studies are available on unenhanced MRI it would be desirable with a meta-analysis on this group of exams as well.

There is no study yet on MRI to detect APE in pregnant patients. It has previously been recommended to avoid MRI during the first trimester, but a recent study on 1.5 million pregnancies exposed to MRI showed no complications during any part of pregnancy (89). This opens up for a study on unenhanced MRI in pregnant patients, which has a number of potential benefits. To start with, it offers a radiation free option to V/Q scan and CTPA. Just like CT MRI shows direct signs of APE and it is also able to detect severe differential diagnoses such as aortic dissection. Compared to CT there is no need to time a contrast bolus why it is possible that MRI might give a higher diagnostic yield than CTPA and V/Q scan.

Currently, it is likely that we will see a clinical introduction of MRI in patients unsuitable for CTPA in the upcoming years. Nevertheless, it is possible that MRI over time will replace CTPA as the first line investigation in patients with suspected APE. However, the general availability of MRI in emergency settings must be improved first and the image acquisition must become faster.

Concerning CTEPH, the 2015 ESC/ERS guidelines on pulmonary hypertension stated that CT is a widely available method that may suggest a diagnosis of PH and identify potential causes (10). The 2019 ESC guidelines on APE briefly mention CTEPH and identify CTPA as

a method that is “gaining ground” although VQ scan remains the first-line imaging modality (15). However, V/Q scans are recommended for screening and it is emphasised that most patients require conventional pulmonary angiography for presurgical assessment. In *Study III* we found a high sensitivity for CT in CTEPH patients and it is possible that CT will replace VQ-scans and conventional angiography in the future. Most patients with suspected CTEPH will have had a thoracic CT according to guidelines and we would consider that this is re-evaluated at an expert centre as a first screening before ordering a VQ-scan. Nevertheless, further and preferably larger scale studies on CT’s diagnostic capability will be required. It would also be useful to compare CT-findings with conventional angiographic findings and surgical specimens to document the methods usefulness in the pre-surgical evaluation.

If CT is to be introduced in larger scale regarding CTEPH patients it is important to improve the knowledge of CTEPH findings in the imaging community. How this is best achieved can be investigated in future studies on training programs among radiologists and residents. However, it is likely that training programs using deliberate practice or similar self-directed programs will be used to a larger extent in the future. There are already online training courses for radiologists using similar methods, one example being the TMC Academy image reporting simulator (92). There have been information campaigns abroad about CTEPH that potentially could be applied in Sweden as well.

Hopefully, increased use of CT in the diagnostic work up of CTEPH patients and improved awareness of the condition will lead to earlier detection and diagnosis, with improved prognosis over time.

8 SVENSK SAMMANFATTNING (ABSTRACT IN SWEDISH)

Bakgrund: Akut lungemboli är ett potentiellt allvarligt medicinskt tillstånd med blodproppar i lungartärerna. För det mesta brukar lungembolier upplösas utan komplikationer efter blodförtunnande behandling. Hos vissa patienter försvinner inte propparna och de kvarstående resterna orsakar ett ökat tryck i lungkärlen, ett tillstånd som är känt som kronisk lungembolisering, vilket medför sänkt kondition och andnöd för de drabbade. Både akuta och kroniska lungembolier har en ospecifik symtombild och bilddiagnostik är avgörande för att ställa rätt diagnos. Beträffande akuta lungembolier är datortomografi (DT) av lungartärerna referensmetod och kliniskt förstahandsval men metoden lämpar sig inte för alla patienter. DT har en hög specificitet för kronisk lungembolism men sensitiviteten är i nuläget oklar. För närvarande rekommenderas inte DT som ett förstahandsval för att utesluta kronisk lungembolism.

Syfte: Att undersöka ännu ej etablerade bilddiagnostiska metoder för att ställa diagnoserna akut (*Studie I*) och kronisk lungemboli (*Studie III*) inklusive inlärningsaspekter (*Studie II*) och aktuell kunskapsnivå (*Studie IV*) hos röntgenläkare. Avseende akut lungembolism studerade vi magnetresonanstomografi (MR) och beträffande kronisk lungembolism DT.

Material och metoder: *Studierna I-II* baserades på ett prospektivt material om 70 MR-undersökningar utan kontrastmedel med DT som referensmetod. I *Studierna III-IV* användes ett retrospektivt material om 43 DT-undersökningar från patienter med konstaterad kronisk embolisering samt en matchad kontrollgrupp med akut lungembolism.

Resultat: Samtliga MR-undersökningar var av diagnostisk kvalitet. Specificiteten var 100% för båda granskarna och sensitiviteten var 90% respektive 93% med i det närmaste perfekt överrensstämmelse mellan granskarna, kappa 0.97 (*Studie I*). ST-läkarna som genomgick ett träningsprogram avseende MR-undersökningar nådde en kliniskt acceptabel nivå efter ca 50 undersökningar och granskningstiden halverades under träningsprogrammet (*Studie II*). Sensitiviteten och specificiteten för kronisk lungembolisering med DT granskat av två subspecialiserade radiologer var 100% (*Studie III*), medan sensitiviteten baserat på originalutlåtandena från samma undersökningar endast var 26% (*Studie IV*).

Slutsats: MR utan kontrastmedel har en hög sensitivitet och specificitet för akut lungembolism (*Studie I)* och ST-läkare kan lära sig att granska sådana undersökningar genom ett träningsprogram (*Studie II*). DT lungartärer har en hög sensitivitet vid granskning av subspecialiserade röntgenläkare (*Studie III*), men bland allmänradiologer är sensitiviteten låg (*Studie IV*).

9 ACKNOWLEDGEMENTS

I wish to express my deepest gratitude to everyone who made this thesis possible.

My main supervisor **Peter Lindholm**, for taking time every time! For always making our projects the priority in your busy schedule. For generous advise in science, work and life on the whole. I feel truly lucky to have had such a dedicated main supervisor.

My co-supervisor **Sven Nyrén** for your creativity and constant optimism. For introducing me to such an interesting research topic.

My co-supervisor **Eli Westerlund** for sharing your vast and valuable clinical knowledge in the thromboembolic field. You have become more than a supervisor. Someone to trust and confide in. Someone who makes me believe in myself and to always aim just a bit higher.

To my formal mentor **Marika Lidegran** for support in the beginning of my period as a PhD student.

To **Deepa Gopalan** for your efforts with the CTEPH studies and for being such an inspiring role model.

To **Lennart Blomqvist** for creating a good scientific atmosphere at the radiology department.

To all my colleagues at FO thoraxradiologi: **Kerstin**, **Louise**, **Eva**, **Ann-Marie**, **Hanna**, **Åke**, **Bo**, **Staffan**, **Jacek** and **Vitali** for generously sharing their extensive knowledge in thoracic radiology, for covering for me when working on this thesis and for friendship and support.

To everyone at the radiology department in Norrtälje for their patience and kindness, especially to my fellow radiologists **Tatiana**, **Gunnar**, **Staffan**, **Istvan**, **Johan**, **Bojan** and **Prathap** for taking me on and teaching me radiology. You will always have a special place in my heart!

To **Paula Toumie,** what would we have done at the department of thoracic radiology without you!

To **Mikael Lindberg** for kind assistance in the detective work of finding exams, blinding exams and technical support.

To **Roberto Vargas** for his great enthusiasm and for always pushing me to understand more about MRI.

To the staff at the department of Physiology and Pharmacology, in particular **Sofia Pettersson** and **Eddie Weitzberg** for all their guidance and help with practical matters.

To **Per Näsman**, KTH, for interesting discussions on study design and guidance in the world of statistics.

To everyone at Unilabs Sophiahemmet Röntgen for the warm welcome and covering for me while finishing this thesis, in particular **Helene**, **Lotta**, **Staffan**, **Istvan**, **Per** and **Karin**.

To my dear friends from medical school: **Daniela, Lena, Rosie and Hamid** for being there all the way.

To my parents-in-law **Görel** and **Jan** for their love and support.

To my parents **Louise** and **Gunnar** for their love and support. For encouraging my eagerness to learn and for early on providing me with the best possible educational options.

Finally but not least to **Jonas,** the love of my life, my best friend and a truly kindered spirit. And also for giving me **John** and **Lovisa**.

10 REFERENCES

1. Virchow R. Gesammelte Abhandlungen. 1856.

2. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012;379:1835-1846.

3. Bounameaux H, Perrier A, Righini M. Diagnosis of venous thromboembolism: an update. Vascul Med. 2010;15:399-406.

4. Konstantinides SV, Torbicki A, Agnelli G et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35:3033-3069, 69a-69k.

5. Francois CJ, Hartung MP, Reeder SB et al. MRI for acute chest pain: current state of the art. J Magn Reson Imaging. 2013;37:1290-1300.

6. Zhou M, Hu Y, Long X et al. Diagnostic performance of magnetic resonance imaging for acute pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost. 2015;13:1623-1634.

7. Davidson BL, Lacrampe MJ. Why can't magnetic resonance imaging reliably diagnose pulmonary embolism? Ann Intern Med. 2010;152:467-468.

8. Castaner E, Gallardo X, Ballesteros E et al. CT diagnosis of chronic pulmonary thromboembolism. Radiographics. 2009;29:31-50.

9. Dronkers CE, Klok FA, Huisman MV. Current and future perspectives in imaging of venous thromboembolism. J Thromb Haemost. 2016;14:1696-1710.

10. Galie N, Humbert M, Vachiery JL et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Heart J. 2016;37:67-119.

11. McNeil K, Dunning J. Chronic thromboembolic pulmonary hypertension (CTEPH). Heart. 2007;93:1152-1158.

12. Gopalan D, Delcroix M, Held M. Diagnosis of chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2017;26(143).

13. Bagalas V, Paspala A, Sourla E et al. Chronic thromboembolic pulmonary hypertension: do not miss the chance for an early diagnosis. Am J Case Reports. 2014;15:378-381.

14. Tureli D, Altas H, Cengic I et al. Utility of Interobserver Agreement Statistics in Establishing Radiology Resident Learning Curves During Self-directed Radiologic Anatomy Training. Acad Radiol. 2015;22:1236-1241.

15. Konstantinides SV, Meyer G, Becattini C et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2019;41:543-603.

16. Socialstyrelsen/Swedish National Board of Health and Welfare.. Socialstyrelsens riktlinjer för vård av blodpropp/venös tromboembolism 2004. Available at:

http://www.alvsbyn.se/wp-content/uploads/2014/03/2004-102-3_20041023.pdf2004 (accessed 2016-08-29).

17. Socialstyrelsen/Swedish National Board of Health and Welfare. Socialstyrelsens statistikdatabas. Available at: http://www.socialstyrelsen.se/statistik/statistikdatabas/diagnoserislutenvard (accessed 2020-01-30).

18. Limbrey R, Howard L. Developments in the management and treatment of pulmonary embolism. Eur Respir Rev. 2015;24:484-497.

19. Meyer G, Planquette B, Sanchez O. Pulmonary embolism: whom to discharge and whom to thrombolyze? J Thromb Haemost. 2015;13.

20. Timp JF, Braekkan SK, Versteeg HH et al Epidemiology of cancer-associated venous thrombosis. Blood. 2013;122:1712-1723.

21. Abdol Razak NB, Jones G, Bhandari M et al. Cancer-Associated Thrombosis: An Overview of Mechanisms, Risk Factors, and Treatment. Cancers. 2018;10

22. Kearon C, Akl EA. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. Blood. 2014;123:1794-1801.

23. Guerin L, Couturaud F, Parent F et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. Thromb Haemost. 2014;112:598-605.

24. Pengo V, Lensing AW, Prins MH et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004;350:2257-2264.

25. Klok FA, Dzikowska-Diduch O, Kostrubiec Met al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost. 2016;14:121-128.

26. Pepke-Zaba J, Delcroix M, Lang I et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011 ;124:1973-1981.

27. D'Armini AM. Diagnostic advances and opportunities in chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2015 (136):253-262.

28. Wang RC, Bent S, Weber E et al. The Impact of Clinical Decision Rules on Computed Tomography Use and Yield for Pulmonary Embolism: A Systematic Review and Meta-analysis. Ann Emerg Med. 2016;67:693-701.

29. Agnelli G, Becattini C. Acute pulmonary embolism. New Engl J Med. 2010;363:266-74.

30. Wells PS, Anderson DR, Rodger M et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416-420.

31. internetmedicin.se. Lungemboli. Available at: http://www.internetmedicin.se/page.aspx?id=199. (Accessed 2020-01-18).

32. van der Pol LM, Tromeur C, Bistervels IM, et al. Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. New Engl J Med. 2019;380:1139-1149.

33. Clemens S, Leeper KV, Jr. Newer modalities for detection of pulmonary emboli. Am J Med. 2007;120:S2-12.

34. Righini M, Kamphuisen PW, Le Gal G. Age-adjusted D-dimer cutoff levels and pulmonary embolism-reply. Jama. 2014;312:557-558.

35. Righini M, Nendaz M, Le Gal G et al. Influence of age on the cost-effectiveness of diagnostic strategies for suspected pulmonary embolism. J Thromb Haemost. 2007;5:1869-1877.

36. Yazdani M, Lau CT, Lempel JK et al. Historical Evolution of Imaging Techniques for the Evaluation of Pulmonary Embolism. Radiographics 2015;35:1245-62.

37. Stein PD, Henry JW, Gottschalk A. Reassessment of pulmonary angiography for the diagnosis of pulmonary embolism: relation of interpreter agreement to the order of the involved pulmonary arterial branch. Radiology. 1999;210:689-691.

38. Remy-Jardin M, Pistolesi M, Goodman LR et al. Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner Society. Radiology. 2007;245:315-329.

39. Memon HA, Lin CH, Guha A. Chronic Thromboembolic Pulmonary Hypertension: Pearls and Pitfalls of Diagnosis. Methodist Cardiovasc J. 2016;12:199-204.

40. Stein PD, Athanasoulis C, Alavi A et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. Circulation. 1992;85:462-468.

41. Henry JW, Relyea B, Stein PD. Continuing risk of thromboemboli among patients with normal pulmonary angiograms. Chest. 1995;107:1375-1378.

42. Goodman LR. Small pulmonary emboli: what do we know? Radiology. 2005;234:654-658.

43. Investigators P. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). Jama. 1990;263:2753-2759.

44. Bajc M, Neilly JB, Miniati Met al. EANM guidelines for ventilation/perfusion scintigraphy : Part 1. Pulmonary imaging with ventilation/perfusion single photon emission tomography. Eur J Nucl Med Molecul Imaging. 2009;36:1356-1370.

45. Roach PJ, Schembri GP, Bailey DL. V/Q scanning using SPECT and SPECT/CT. J Nucl Med. 2013;54:1588-1596.

46. Ruggiero A, Screaton NJ. Imaging of acute and chronic thromboembolic disease: state of the art. Clin Radiol. 2017;72:375-388.

47.Remy-Jardin M, Remy J, Wattinne L et al. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-hold technique-comparison with pulmonary angiography. Radiology. 1992;185:381-387.

48. Stein PD, Fowler SE, Goodman LR et al. Multidetector computed tomography for acute pulmonary embolism. New Engl J Med. 2006;354:2317-2327.

49. Bergin CJ, Sirlin CB, Hauschildt JPet al. Chronic thromboembolism: diagnosis with helical CT and MR imaging with angiographic and surgical correlation. Radiology. 1997 ;204:695-702.

50. Tunariu N, Gibbs SJ, Win Z et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med. 2007;48:680-684.

51. Reichelt A, Hoeper MM, Galanski M et al. Chronic thromboembolic pulmonary hypertension: evaluation with 64-detector row CT versus digital substraction angiography. Eur J Radiol. 2009;71:49-54.

52. Rajaram S, Swift AJ, Telfer A et al. 3D contrast-enhanced lung perfusion MRI is an effective screening tool for chronic thromboembolic pulmonary hypertension: results from the ASPIRE Registry. Thorax. 2013;68:677-678.

53. Ley S, Ley-Zaporozhan J, Pitton MBet al. Diagnostic performance of state-of-the-art imaging techniques for morphological assessment of vascular abnormalities in patients with chronic thromboembolic pulmonary hypertension (CTEPH). Eur Radiol. 2012;22:607-616.

54. He J, Fang W, Lv B et al. Diagnosis of chronic thromboembolic pulmonary hypertension: comparison of ventilation/perfusion scanning and multidetector computed tomography pulmonary angiography with pulmonary angiography. Nucl Medicine Comm. 2012;33:459-463.

55. Ley S, Kauczor HU, Heussel CP et al. Value of contrast-enhanced MR angiography and helical CT angiography in chronic thromboembolic pulmonary hypertension. Eur Radiol. 2003;13:2365-2371.

56. Expert Panels on C, Thoracic I, Kirsch J, Brown RKJ, Henry TS, Javidan-Nejad C, et al. ACR Appropriateness Criteria((R)) Acute Chest Pain-Suspected Pulmonary Embolism. J Am Coll Radiol. 2017;14:S2-S12.

57. Wittram C, Maher MM, Yoo AJ et al. CT angiography of pulmonary embolism: diagnostic criteria and causes of misdiagnosis. Radiographics. 2004;24:1219-1238.

58. Gillespie C, Foley S, Rowan M et al. The OPTICA study (Optimised Computed Tomography Pulmonary Angiography in Pregnancy Quality and Safety study): Rationale and design of a prospective trial assessing the quality and safety of an optimised CTPA protocol in pregnancy. Thromb Res. 2019;177:172-179.

59. Hochhegger B, Marchiori E, Irion K et al. Magnetic resonance of the lung: a step forward in the study of lung disease. J Bras Pneumo. 2012;38:105-115.

60. Hochhegger B, Ley-Zaporozhan J, Marchiori E et al. Magnetic resonance imaging findings in acute pulmonary embolism. Br J Radiol. 2011;84:282-287.

61. 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 Zeitschrift fur Gefasskrankheiten. 2016;45:149-154.

62. Revel MP, Sanchez O, Lefort C et al. Diagnostic accuracy of unenhanced, contrast-enhanced perfusion and angiographic MRI sequences for pulmonary embolism diagnosis: results of independent sequence readings. Eur Radiol. 2013 Sep;23:2374-2382.

63. Benson DG, Schiebler ML, Nagle SK et al. Magnetic Resonance Imaging for the Evaluation of Pulmonary Embolism. Top Magn Reson Imaging. 2017 ;26:145-151.

64. 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;152:434-443.

65. 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;10:743-750.

66. Nikolaou K, Schoenberg SO, Attenberger U et al. Pulmonary arterial hypertension: diagnosis with fast perfusion MR imaging and high-spatial-resolution MR angiography-preliminary experience. Radiology. 2005;236:694-703.

67. Bin Saeedan M, Alabdulkarim FM, Aloufi FF et al. Check the chest: review of chest findings on abdominal MRI. Clin Imaging. 2020;59:68-77.

68. Mitchell AM, Kline JA. Contrast nephropathy following computed tomography angiography of the chest for pulmonary embolism in the emergency department. J Thromb Haemost. 2007;5:50-54.

69. Ridge CA, McDermott S, Freyne BJ et al. Pulmonary embolism in pregnancy: comparison of pulmonary CT angiography and lung scintigraphy. Am J Roentgenol. 2009 ;193:1223-1227.

70. Bordeleau S. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 2: Imaging for the diagnosis of pulmonary embolism in pregnant women. Emerg Med J. 2013;30:251-252.

71. Kilty C, Wiese A, Bergin C et al. A national stakeholder consensus study of challenges and priorities for clinical learning environments in postgraduate medical education. BMC Medical Education. 2017;1:226.

72. Hodges BD. A tea-steeping or i-Doc model for medical education? Acad Med. 2010;85:S34-44.

73. Pock AR, Durning SJ, Gilliland WR et al. Post-Carnegie II curricular reform: a north American survey of emerging trends & challenges. BMC Medical Education. 2019;19:260.

74. Pusic M, Pecaric M, Boutis K. How much practice is enough? Using learning curves to assess the deliberate practice of radiograph interpretation. Acad Med. 2011;86:731-736.

75. Hastings RH, Rickard TC. Deliberate practice for achieving and maintaining expertise in anesthesiology. Anesth Analg. 2015;120:449-459.

76. Ericsson K A KRT, Tesch-Römer C. The Role of Deliberate Practice in the Acquisition of Expert Performance. Psychol Rev. 1993;100:363-406.

77. Dachman AH, Kelly KB, Zintsmaster MP et al. Formative evaluation of standardized training for CT colonographic image interpretation by novice readers. Radiology. 2008;249:167-177.

78. Yang HK, Ko Y, Lee MH et al. Initial Performance of Radiologists and Radiology Residents in Interpreting Low-Dose (2-mSv) Appendiceal CT. Am J Roentgenol. 2015;205:W594-611.

79. Williamson KB, Gunderman RB, Cohen MD et al Learning theory in radiology education. Radiology. 2004;233:15-18.

80. Ripsweden J, Mir-Akbari H, Brolin EB et al. Is training essential for interpreting cardiac computed tomography? Acta Radiol. 2009;50:194-200.

81. Joshi R, Wu K, Kaicker J et al. Reliability of on-call radiology residents' interpretation of 64-slice CT pulmonary angiography for the detection of pulmonary embolism. Acta Radiol. 2014;55:682-690.

82. Kalb B, Sharma P, Tigges S et al. MR imaging of pulmonary embolism: diagnostic accuracy of contrast-enhanced 3D MR pulmonary angiography, contrast-enhanced low-flip

angle 3D GRE, and nonenhanced free-induction FISP sequences. Radiology. 2012;263:271-278.

83. Ohno Y, Higashino T, Takenaka D et al. MR angiography with sensitivity encoding (SENSE) for suspected pulmonary embolism: comparison with MDCT and ventilation-perfusion scintigraphy. Am J Roentgenol. 2004;183:91-98.

84. Edelman RR, Silvers RI, Thakrar KH et al. Nonenhanced MR angiography of the pulmonary arteries using single-shot radial quiescent-interval slice-selective (QISS): a technical feasibility study. J Cardiovasc Magn Reson. 2017;19:48.

85. Pasin L, Zanon M, Moreira J et al. Magnetic Resonance Imaging of Pulmonary Embolism: Diagnostic Accuracy of Unenhanced MR and Influence in Mortality Rates. Lung. 2017;195:193-199.

86. MedCalc. MedCalc Software. Available at: https://http://www.medcalc.org. (Accessed 2015-11-11)

87. GraphPad. GraphPad Software. Available at: https://www.graphpad.com (Accessed 2015-11-11).

88. Grobner T. Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant. 2006 ;21:1104-1108.

89. Ray JG, Bharatha A, Montanera WJ. Magnetic Resonance Imaging Exposure During Pregnancy-Reply. Jama. 2016;316:2275-2276.

90. Kearon C, Akl EA, Ornelas J et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149:315-352.

91. Schiebler ML, Nagle SK, Francois CJ et al. Effectiveness of MR angiography for the primary diagnosis of acute pulmonary embolism: clinical outcomes at 3 months and 1 year. J Magn Reson Imaging. 2013;38:914-925.

92. TMC Academy. Image Reporting Simulator. Available at: https://academy.telemedicineclinic.com (Accessed 2020-03-08)