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Computer-Aided Detection, Pulmonary Embolism, Computerized Tomography Pulmonary Angiography: Current Status

Abdel-Razzak M. Al-hinnawi

Abstract

Angiography (mostly computed tomography, but in some cases, conventional) is still the gold diagnostic standard in the clinical diagnosis of pulmonary embolism (PE). Computer-aided detection (CAD) is software that alerts radiologists the presence of PE during computerized tomography pulmonary angiography (CTPA) examinations. Interpreting CTPA scans with the aid of commercially available CTPA-CAD has improved the detectability of PE patients. This chapter aims to complete the scope of this book by explaining the clinical evidences of PE, the CTPA technology, the role of CTPA-CAD software in improving the diagnostic abilities of CTPA and the role of conventional pulmonary angiography in daily clinical practice. The reader will be introduced to the performance of diagnosing PE with or without the aid of CTPA-CAD algorithms. Differences among CTPA-CAD's output will be compared and tabled according to "per patient," "per clot," "first reader," and "second reader" basis. This includes, but not limited to, the CTPA-CAD's sensitivity and specificity in comparison to human observer performance (i.e., radiologist). These topics cover the *current status* practice at the pulmonary angiography clinic.

Keywords: computer-aided detection, computerized tomography pulmonary angiography, pulmonary embolism, digital image processing, conventional pulmonary angiography

1. Introduction

Computer sciences have reached medicine [1]. This includes developing algorithms to participate in the clinical interpretation of medical images acquired from various medical

imaging systems [2, 3]. These algorithms are categorized into two main groups. They are the computer-aided detection (CAD) and the computer-aided diagnosis (CADx) [2, 3]. Both of them employ principles of digital image processing (DIP).

Pulmonary embolism (PE) is the partial or complete blockage of one or some of pulmonary arteries; it is a life threatening disease with a challenging diagnosis [4]. In Europe and the USA, it leads to high incidence of mortality, morbidity, and hospitalization [4, 5]. Internationally, PE is expected to become the third leading cause of death by 2030 according to clinical projections on disease mortality [6]. Computerized tomography pulmonary angiography (CTPA) has become the first-line imaging examination to detect the occurrence of PE [4, 7–9]. Clinical trials of CTPA examination, without the aid of CAD, reported that the sensitivity and specificity CTPA scan may not reach 100% [8, 10]. This indicates that misdiagnoses, which are a prospective health burden and potential life threatening, may occur.

This chapter describes the current state of PE diagnosis in CTPA clinic, with and without the use of CAD algorithms. The chapter is divided into three main sections. Section 2 presents all clinical evidences about the PE as a disease that threaten lives. This covers the PE epidemiology, incidence rate, characterizations, load scores, diagnosis, and treatment. Section 3 is dedicated to explain the CTPA physics and technology, image appearance, PE radiographic features, clinical trials, and common artifacts. Section 4 explains the art of computer-assisted detection and its applications in diagnosing PE. This demonstrates the role of CAD software in improving the PE diagnosis. In general, this chapter provides the up-to-date knowledge of PE diagnosis in angiography clinics.

2. Pulmonary embolism

2.1. Definition

Pulmonary embolism (PE) occurs when a blood clot, also known as a thrombus or embolus, arrives to pulmonary arteries. The source of thrombus is likely to be large veins of the lower extremity before it migrates through venous system to reach first the right heart chambers and later the lungs (**Figure 1**). Once a clot arrives to pulmonary arterial tree, it travels in the arteries of the lung until it blockades vessel/s that is/are too narrow to continue further. Thus, PE happens (**Figure 1**) leading to pulmonary blood flow shortage. Consequently, this condition associates with rise in the artery pressure due to the increased resistance to the bloodstream, shortness of breath, chest pain, and breathing difficulties; it can also lead to infarct or decrease in cardiac output, which in turn can cause hemodynamic disturbances, heart failure or even death [4, 5, 11, 12]. The common risk factors for PE are immobility or inactivity, hypertension, surgery or trauma, cigarette smoking, obesity, heart failure, cancer, chronic obstructive lung disease, hormone therapy, pregnancy, and advanced age and family members with thrombosis or embolism [4, 5, 12].

2.2. Incidence

Clinical surveys showed that the PE exhibits the highest incidence of mortality, morbidity, and hospitalization [4, 5, 13, 14]. The incidence of PE vary from one country to other but this
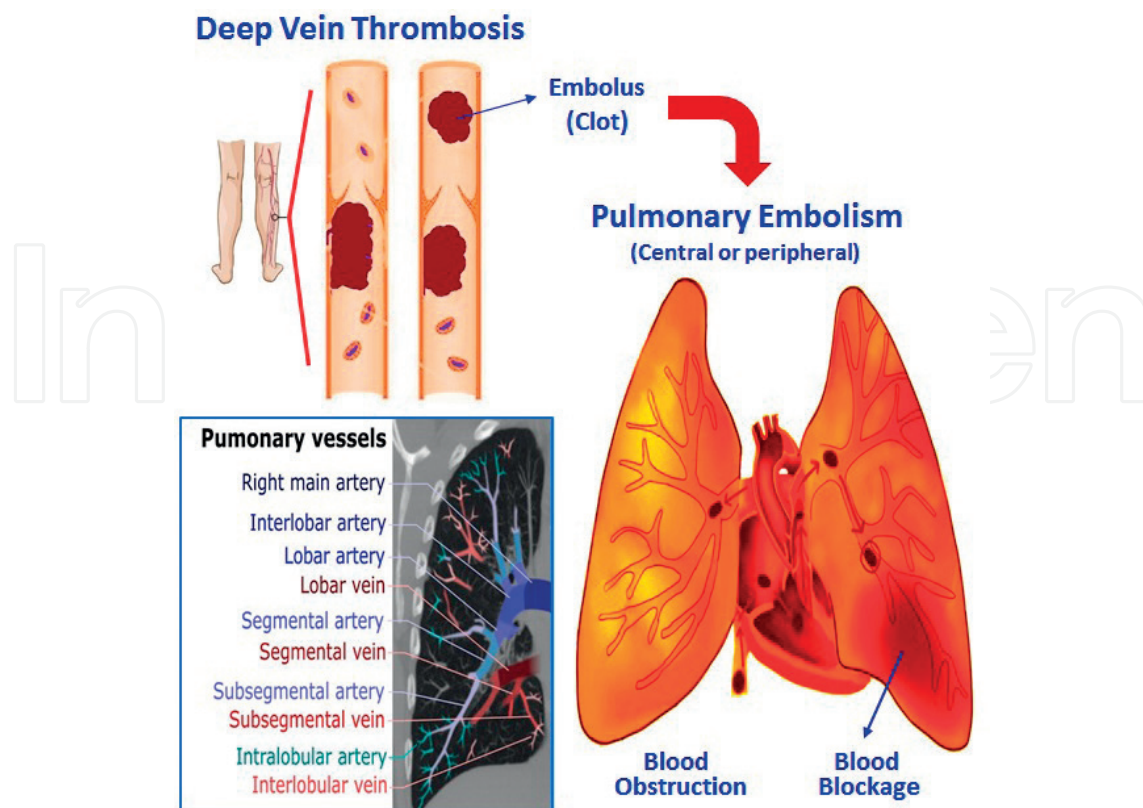
Figure 1. Pulmonary embolism pathophysiology.

variation is likely attributed to the type and accuracy of the diagnostic procedure rather than the actual incidence of the disease itself [6, 15–18]. Annually, there are 430,000 and 300,000 to 600,000 PE conditions in Europe and the USA, respectively [15, 16]. Globally, the clinical projections of mortality estimate that the incidence of PE will be the third major cause of death in year 2030 [6]. In Europe and the USA, autopsy investigations on hospitalized patients showed a PE prevalence from 60 to 70% [4, 5]. Therefore, the precise detection and diagnosis are highly desirable [4, 5].

2.3. Characterization

Embolus is characterized as central or peripheral, based on the site of the affected blood vessel branch [4]. Central vascular regions include the left and right main pulmonary arteries (PA), the right and left interlobar arteries, the right and left lobar arteries, and right and left lobar veins (**Figure 1**). Peripheral vascular regions include the remaining blood vessels in the upper, middle, and lower lobes of the right lung; and the upper and lower lobes in the left lung. This includes all the segmental, subsegmental, and intralobular arteries and veins including the culmen and the lingual (**Figure 1**).

Once a thrombus has been identified in the PA, it is further characterized as acute or chronic, as illustrated in **Figure 2** [4]. In some cases, there is doubt between those two classes, depending on diagnosis procedure and experience of the observer. A clot in PA is usually considered as being "acute" if it is located centrally within the vascular lumen. This may lead to vessel dilation. However, a clot in PA is characterized as "chronic" when it appears contiguous to

Figure 2. Illustration of acute and chronic PE.

the vessel wall substantially reducing the arterial diameter. A clot that exhibits caves or canals within itself is also considered as "chronic."

2.4. Load scores

Several scoring systems have been introduced to measure the severity of the PE clinic. For central PE, physicians utilize the Walsh, Miller, Qanadli, or Mastora score. While for peripheral PE, they use Marder, Arnesen, Mewissen (American Venous Registry), Porter, Ouriel, or Bjorgell scores. They are well summarized by Ghaye et al. [19, 20]. All these scores depend on the number of clots, location, and the percentage of obstruction. They all verified appropriate for assessing the severity of PE and treatment effectiveness, but are not much used in angiography clinics due to time it takes to manually assess them.

2.5. Diagnosis

Diagnosing PE remains a challenge to physicians because the symptoms are unspecific and may not be present in all patients. The PE symptoms and risk factors (Section 2.1) are used to determine the probability of PE. Although biomarkers and laboratory tests are crucial to estimate the probability of PE, such as the electrocardiogram (ECG) and the measurement of percentage of cross-linked fibrin in the blood (D-dimer), the diagnostic decision is always based on radiographic findings from medical imaging procedures [4]. Different medical imaging techniques exist to "rule in" or "rule out" the presence of the PE. Each technique exhibits its strength and weakness and a shift toward the computerized tomography (CT) has been approved.

A planner chest X-ray remains the first imaging step because it can rule out the conditions that mimic PE (e.g., a pneumothorax can cause chest pain similar to pain caused by acute PE), but it cannot exclude PE. Another X-ray imaging test is the lower extremity venous angiography, in which contrast media is injected via a foot vein, and several X-ray projections contrast-filled leg veins are taken [4]. The leg veins are "opacified" with contrast media, indicating the site of blood flow obstruction due to thrombosis. In both diagnosis situations, that is venous thrombosis is ruled in or out, further medical imaging tests are required to assess the decision of PE, which implies burden and probably additional radiation dose to patient.

Nuclear medicine techniques (e.g., pulmonary ventilation perfusion scintigraphy) permit the visualization of the distribution of a radioactive substance (i.e., radiopharmaceutical) through planner gamma camera or single photon emission computerized tomography (SPECT) [21, 22]. In this technique, after the administration of gamma ray isotope tracer, the observation of airways and pulmonary blood vessels activity is made, hence the name, ventilation/perfusion

(V/Q) scan. This scan remained as the traditional preferred imaging technique before the shift toward CT [4]. A mismatch of ventilated but not perfused lung tissue was considered as indicator for pulmonary embolism. Thus, it is indirect detection of an embolus by looking at the effects of an occlusion. A normal perfusion scan securely excluded pulmonary embolism, but was found in a minority of the patients that are suspected of PE, and thus, often further testing was needed [4]. The advantages of V/Q scan are that it is not invasive and less irradiant than CT, and may be more suitable for patients that are allergic to iodinated agents (CT). Its disadvantage is that the obtained image determines only regions of the lungs that are not correctly vascularized, nonobstructing "small" clots remaining invisible [4]. Moreover, the duration of the exam is in the order of 20 min, which is slower than other modalities. Several reports showed that the CT scan outweigh the V/Q scan by performing both lower rate of false-negative scans and lower number of "indeterminate scans" not yielding a definite diagnosis [4, 22].

The sequence of chest X-ray projections during the administration of contrast agent directly into the target vessels, also called as pulmonary angiography, is a reliable test for diagnosing PE. In this imaging scan, a catheter is inserted into a femoral vein and navigated through the heart toward the pulmonary arteries. Amounts of contrast media is injected several times at various locations of pulmonary vessels, and sequence of X-ray planner projections are obtained. It is used to provide a definitive diagnosis when other imaging tests fail [4]. Although conventional pulmonary angiography has great value in PE diagnosis, it suffers from being expensive, invasive with serious side effect, requiring expertise and supporting staff, and not readily available in most hospitals.

Vascular Doppler ultrasound is a quick, noninvasive, and reliable technique [23]. It is painless and carries no risk. However, it provides less clinical information (e.g., number of clots and amount of obstruction) than other imaging techniques and very dependent on the experience of the examiner [4, 23].

Finally, several reports showed promising results for the assessment of PE with magnetic resonance imaging (MRI) [24, 25]. This modality is promising because images can be generated without radiation, and because it allows a combination of morphological and functional imaging (e.g., perfusion). However, MR has a lower spatial resolution than CT and much longer acquisition times (around 30 min as opposed to seconds in CT).

2.6. Treatment

Untreated PE can be fatal with high mortality rate that can be decreased under rapid detection [6]. There are ranges of different types of treatment procedures [4]. They include hemodynamic and respiratory support, anticoagulation medications, thrombolytic therapy, surgical embolectomy, percutaneous catheter-directed therapy, and venous filter intervention, which are not without complications. The selection of treatment depends on the PE severity and prognosis. Generally, the obstruction is mild when only a few subsegmental vessels are blocked and it is severe when multiple segmental or a few lobar vessels are blocked. Mild PE is managed with clot-dissolving medication. Severe PE requires additional medical intervention, such as placement of a filter in the inferior vena cava, or clot removal with either a catheter or surgery.

2.7. Summary

This section introduced clinical facts of pulmonary embolism. This includes concise of PE's epidemiology, predisposing factors, pathophysiology, classifications, and treatments procedures. The available diagnostic medical imaging systems, which are the decision-makers of the presence and severity of PE, were explained with their strengths and limitations, rationalizing the shift toward the use of CT.

3. Computerized tomography pulmonary angiography (CTPA)

Computerized tomography pulmonary angiography (CTPA) is a multidetector computerized tomography (MDCT) scanner that acquires cross-sectional chest images during the administration of contrast agent [10]. This permits the visualization of the blood flow in pulmonary veins and arteries. This section describes the CTPA technology and its impact in diagnosing PE. Aspects covered include: (1) the basic of CTPA technology, (2) the CTPA radiographic appearance, (3) the radiographic features of suspicious PE, and (4) the clinical performance of CTPA scans including sensitivity, specificity, and pitfalls.

3.1. CTPA technology

On CTPA, the patient's chest is exposed by a calibrated X-ray cone beam during the injection of contrast media into patient, as shown in **Figure 3**. The X-ray photons are absorbed (i.e., attenuated) by various structures within the chest. The amount of X-ray attenuations varies with accordance to the type and density of the tissues in the chest. The maximum absorption occurs in the dense bone and sites of contrast agent (i.e., pulmonary vessels); while the minimum absorption happens in the lung (i.e., air); the other thorax tissues (i.e., the heart, the muscles, and the upper parts of abdomen) lay in between those two structures. The X-ray
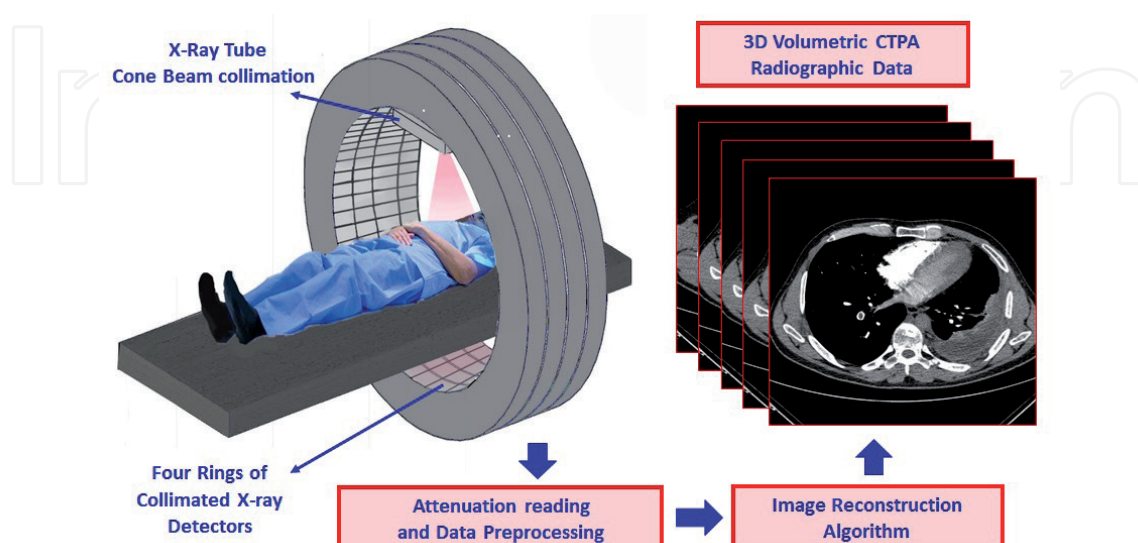

Figure 3. Four rings MDCT technology (there are 256 rings in modern MDCT).

cone beam rotates 360 degrees around the patient. At each angle, the penetrated X-ray beam from patient strikes rings of X-ray digital detectors. The detectors measure the amount of X-ray absorption and then fed to computer which, in turn, processes these data to reconstruct a CTPA three dimensional (3D) volumetric radiographic data of the chest's tissues. The CTPA image quality is governed by set of technical parameters; the interested readers may revise one of the MDCT books such as the book by Seeram in Ref. [26].

The volume of contrast media depends on patient weight, and may vary in [40 mL, 140 mL], also based on the dye concentration. Iodine is commonly used because of its relatively harmless interaction with the body and its solubility; the concentration is usually 250–350 mg/mL. Generally, a 4 or 5 mL/s is injected through a catheter in an antecubital vein. The rate of injection may increase in the advanced generations of MDCT, when acquisition time decreases in order to maintain sufficient iodine concentration within the vessels. The contrast peak happens after 10–25 s depending on the patient. Ideally, the scan should be complete before the radiographic dye reaches the left ventricle in the heart, as this may mean contrast has drained from the pulmonary arteries, or require a larger dose of contrast media.

3.2. CTPA radiographic appearance

The CTPA 3D radiographic data are displayed in three orthogonal views (i.e., Digital images); these are the two dimensional (2D) axial, sagittal, and coronal cross sections (**Figure 4**). In each CTPA view, the pixel brightness (2D picture element) is proportional to amount of X-ray absorption at tiny 3D cube (i.e., voxel) in the patient's chest.

Understanding the radiographic CTPA appearance is important during the detection of PE. The lung parenchyma exhibits the lowest X-ray absorption so it appears as "black" regions clearly delineating the borders of lungs in the CTPA view. The soft tissues (i.e., the heart, muscles, fat, and upper constituents of the abdomen) appear as a radiolucent area (lower X-ray absorption). These regions appear in a form of various radiographic shades of gray levels (i.e., various optical intensities). On contrast, the regions of bones and the contrast agent in the pulmonary vessels are radio-opaque (higher X-ray absorption) and appear as bright (i.e., white) regions. **Figure 4** demonstrates the radiographic appearance of these different tissues where the contrast agent (indicated by red letters "CA") looks brighter than the surrounding lung parenchyma, while remaining thorax constituents look with various intensities.
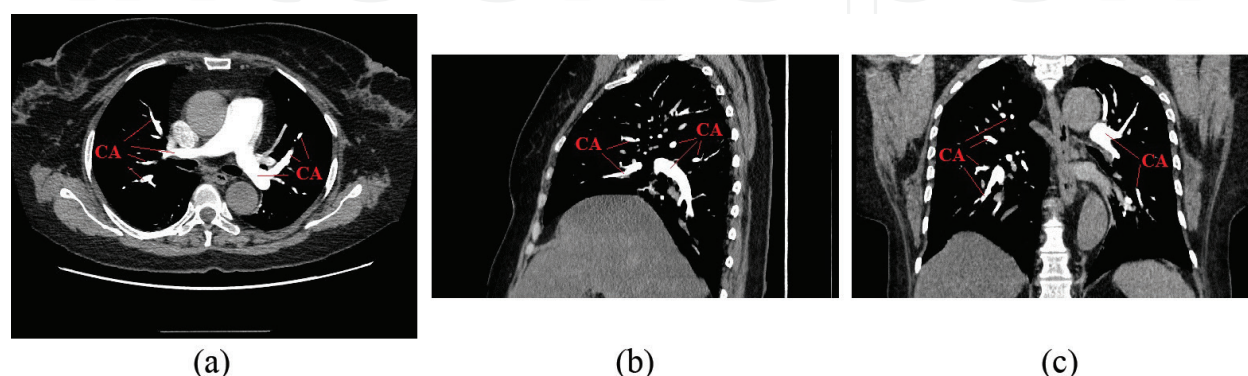

(a)   (b)   (c)

Figure 4. The three CTPA orthogonal views radiographic appearance (axial, sagittal, coronal).

3.3. PE radiographic features

The contrast medium opacifies the bloodstream in the lung. In case of PE, the pulmonary vessel is either completely blocked, or passes around it. Thus, on CTPA view, the veins and arteries appear white where the bloodstream is present, and a thrombus can be observed as a dark spot inside the white mass. **Figure 5** (left) illustrates examples of acute and chronic PE affecting the left main PA and right lobar artery, respectively. Acute thrombi appear as a hole, or concavity, in the vessel, while chronic clots are found on the edge of the vessel, with no concavity. **Figure 5** (right) also shows example of peripheral clot (segmental).

3.4. Clinical performance of CTPA scan

The radiologist navigates the CTPA slices searching the presence of a clot. The diagnosis of PE is categorized in a yes-or-no decision, independent of the location and severity of emboli. When a defect (clot) is found in one slice, the adjacent neighbors are analyzed. The radiologist tracks the clot to the point where she/he knows for sure its anatomical location in the pulmonary vascular veins and arteries and assesses his/her conclusion. Sensitivity and specificity are two statistical parameters commonly used to evaluate any diagnostic test. In this subsection, these two parameters are introduced in association with CTPA examination. This leads to the discussion of the CTPA artifacts.

3.4.1. Terminology background

Let us suppose that a population of patients, pathologically proved to have or not to have PE, was asked to undergo CTPA examination. Then, radiologists are asked to interpret these CTPA scans. The correct interpretation of a CTPA scan can be either a true-positive (TP) response (i.e., the correct detection of clots) or a true-negative (TN) response (i.e., the correct decision that there is no clot). In contrast, the false interpretation of a CTPA scan is described as either a false-positive (FP) response (i.e., the false suggestion of PE that does not exist) or a false-negative (FN) response (i.e., the PE is missed). These four possible categories of CTPA interpretation are illustrated in **Table 1**.

The proportion of TP responses to the total number of pathologically proven PE patients is referred as the true-positive fraction (TPF) or the sensitivity (the ability to detect patients with PE).
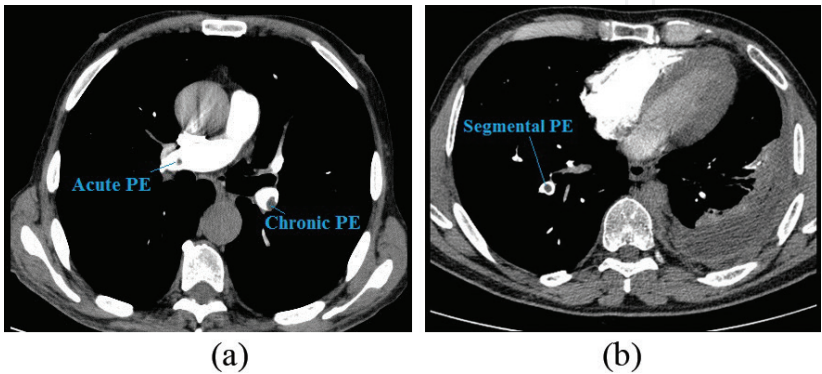

(a)   (b)

Figure 5. Examples of chronic and acute PE (left), and segmental PE (right) appearance on CTPA image.

	CTPA truth information	
Radiologist decision	**Abnormal (PE exists)**	**Normal**
Abnormal	True positive (TP)	False positive (FP)
Normal	False negative (FN)	True negative (TN)

Table 1. Outcomes of radiologist interpretation of CTPA examinations.

It is calculated as the ratio of TPs to the sum of FNs and TPs as illustrated in Eq. (1). On the other hand, the proportion of TN responses to the total number of patients, which do not have PE, is called the true-negative fraction (TNF) or specificity (the ability to exclude patients without PE). It is calculated as the ratio of TNs to the sum of FPs and TNs as illustrated in Eq. (2).

$$sensitivity \ = \ TPF \ = \ \frac{TP}{TP+FN} \tag{1}$$

$$specificity \ = \ \frac{TN}{TN+FP} \tag{2}$$

$$FPF \ = \ \frac{FP}{TN+FP} \ = \ 1-specificity \tag{3}$$

Consequently, sensitivity measures the reader's performance in detecting patients with clots, whereas specificity measures the reader's ability to avoid producing false responses. Specificity is usually derived from the false-positive fraction (FPF) as shown in Eq. (3). Also, the predictive value of a positive test PV(+) and the predictive value of false test PV(−) can be evaluated as in Eqs. (4) and (5). These are also alternatively referred as positive predictive value (PPV) and negative predictive value (NPV). As FP and FN increase (i.e., increment in interpretation mistakes), the PPV and NPV decrease.

$$PV(+) \ = \ \frac{TP}{TP+FP} \tag{4}$$

$$PV(-) \ = \ \frac{TN}{TN+FN} \tag{5}$$

3.4.2. CTPA's sensitivity, specificity, and negative and positive predictive value

Early investigations were reported in the 1990s regarding the impact of CTPA examinations in detecting PE. The results of these reports were reviewed by Rathbun in 2000 [27] and Hiorns in 2002 [28], showing that the sensitivity and specificity of CTPA may vary between the range of 51–100 and 81–100%, respectively. These initial results revealed the possibility of MDCT to diagnose PE.

Over the last decade, the clinical role of CTPA examination has undergone extensive scientific investigations [7–10]. The largest and most significant collaborative clinical trial was conducted in 2006 [10]. This study is well-known as PIOPED II (Prospective investigation of pulmonary

embolism diagnosis, second study). The dataset consisted of 824 patients who had enrolled for CTPA examination in the period 2001–2003 using 4, 8, and 16 rows MDCT devices. These CTPA scans were interpreted by different radiologists at remote clinical centers (i.e., hospitals) in the USA and Canada. The study reported sensitivity (i.e., the proportion of correct diagnosis of patients with PE) of 83% and specificity (i.e., the proportion of the correct diagnosis of patients without PE) of 96%. The high value of sensitivity means high TP and low FN (Eq. (1)), while high value of specificity means high TN and low FP (Eq. (2)). Based on the PE probability is low, intermediate, or high, the PPV and NPV was 58 and 96%, 92 and 89%, and 96 and 60%, respectively. On the other hand, based on the PE location is lobar, segmental, or subsegmental vessels, the PPV was 97, 68, and 25%, respectively. The defects at extreme sites of pulmonary vascular branches (segmental and subsegmental vessels) exhibit less observability, and consequently more challenging to radiologists, than lobar and main PA clots.

A recent report, in 2015, was published by Dogan et al. in the Netherlands; this study reviewed different CTPA clinical trials and reported that the sensitivity and specificity of CTPA scans may vary between the range of 83–100% and 89–96%, respectively [8]. The NPV was 96–99% showing the high CTPA scan's certainty in ruling out PE; *a negative CTPA can safely exclude PE*. Estrada-Y-Martin and Oldham supervised a survey regarding the clinical practice in the diagnosis of PE in USA [9]. The survey included members (i.e., Intervention Radiologists) of the Society of Thoracic Radiology (524 members) and the Society of Interventional Radiologists (389 members). The surveyed members believed that CTPA examination is the gold standard to diagnose PE. This conclusion sustained previous study emphasizing that CTPA is the first-line imaging for the evaluation of PE [7]. These clinical trials and surveys have resulted in the worldwide acceptance of CTPA as the best method for the detection of PE.

3.4.3. CTPA artifacts

Although the clinical reports accepted CTPA as best-reliable method with high sensitivity for diagnosing PE, their results also showed that FNs diagnosis, which are potentially life-threatening or a prospective health burden, may occur. For a radiologist, it can be difficult to detect all PE in the CTPA data [4, 10] for several reasons. In CTPA clinic, the radiologist is asked to examine stack of high resolution 2D CTPA images for single patient. Each 2D CTPA image is a 512 by 512 pixels. The stack builds a 3D CTPA volume of voxels (volume pixels), of which the size, in modern MDCT devices, is approximately 0.6 mm in every direction. Thus, a CTPA scan consists of millions of voxels have to be reviewed. Furthermore, the segmental and subsegmental vascular branches are quit complex; it is impossible to visualize all vascular structures within one CTPA image at a time. Therefore, radiologists usually revise the 3D CTPA volume several times examining only parts of the vascular system in the attempt not to miss an intravascular (sometimes very small) black dot indicating PE. A secure detection or exclusion of PE is therefore quite time-consuming and dependent on the experience of the radiologist.

Additionally, diagnostic pitfalls may occur due to CTPA artifacts [29, 30]. Some artifacts leads to defects that imitate PE; this may include a poorly filled vein with contrast media, lymphoid tissue around the vessels, impacted bronchi mimic dark tubular structures, or parenchymal diseases altering pulmonary perfusion. Technical factors may also lead to artifact hampering the correct PE diagnosis; this include image noise due to low dose or obese patients, respiratory

or cardiac motion leading to inhomogeneous intravascular contrast, streak-artifacts near the superior vena cava due to beam hardening, incorrect timing resulting in insufficient intravascular contrast, or artifacts due to edge-enhancing image reconstruction. Further details of these artifacts are explained in MDCT technical books such as the reference number [26].

3.5. Summary

This section explained the CTPA practice. The CTPA basic physics, technology, examination, and radiographic appearance of PE and other thorax tissues were explained. The sensitivity, specificity, and PPV and NPV of CTPA are outlined based on clinical trials and surveys in the last two decades. These reports concluded that that CTPA remains, at the time, as the first line diagnostic procedure providing the less invasive procedure, and highest sensitivity, specificity, and NPV among other imaging techniques. The CTPA artifacts, which may contribute to misdiagnosis, were mentioned.

4. Computer-aided detection of PE on CTPA views

It is difficult and time consuming for a radiologist to navigate all CTPA orthogonal slices and find all emboli, this also depends on the radiologist experience. In PIOPED II, which was held at well-estimated clinical institutes, the average of 9.3% FP and 2.4 FN responses were reported [10]. This means that among 1000 suspicious PE patients, which is a daily small number of CTPA examination in any developed country, 93 patients may incorrectly diagnosed as having PE and may be asked to undergo further clinical tests, which is a clinical burden and probably additional X-ray radiation dose. Also, which is more critical, 24 patients may be incorrectly excluded of having PE and would leave the hospital without considering medication; these patients would be left under serious medical consequences that may be fatal. It is important to note again that FP and FN depend on radiologist experience, for example, in PIOPED II, it is possible for the NPV and PPV to be 58 and 60%, respectively. This lack of imperfection diagnosis may attribute to many reasons as explained in Section 3.4.3. Therefore, a computer-assisted detection (CAD) for the diagnosis of PE is desirable. This section aims to describe the CAD technology then explains the current state of how PE-CAD can contribute in improving patient health in CTPA clinic. This leads to explain the comments on CAD and the necessary recommendations. Comprehensive information on CAD technology in medical imaging can be found in Ref. [31].

4.1. CTPA-CAD definitions

A computer-aided detection (CAD) algorithm is an architecture of computer image analysis processes that yield, when applied to a CTPA examination, to the prompting of regions of suggestive pulmonary obstruction such as the presence of clots. Such prompting is often used as a "second opinion" to alert the radiologist to structures that, otherwise, might be overlooked [2, 3]. **Figure 6** shows a CTPA slice (left) and the responses of the CTPA-CAD (right), which are indicated as red overlay. They are also called as CAD stimuli, candidates, or outputs. These CTPA-CAD responses are categorized to one of four possible groups, similarly to those explained in Section 3.4.1 describing the radiologist accuracy in interpreting CTPA
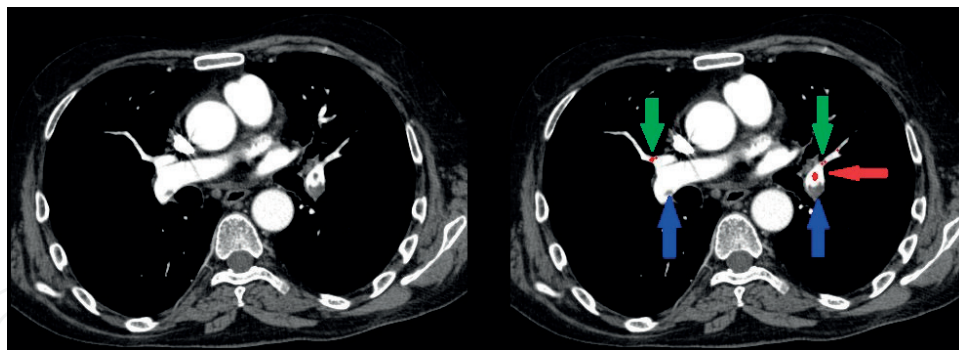
Figure 6. Types of assessment of CTPA-CAD stimuli on CTPA image.

scans. They are: the TP, FP, TN, FNs groups. **Figure 6** (right) illustrates TP (i.e., correct prompt of clot) and FP (incorrect prompt of clot) stimuli, indicated with red and green arrows, respectively. There are two clots that were not prompted, so they are FN stimuli, which are indicated with blue arrow. The remaining pulmonary vessels, which were not prompted as PE, are the TN stimuli. As with radiologist, it is desirable that a CTPA-CAD algorithm leads to the highest TP and TN, while it yields the lowest possible FP and FN stimuli.

The performance of the CAD software can be tested "per clot" or "per patient" basis. For "per clot" basis, the CTPA-CAD responses are counted in comparison to truth of all actual PE occurrences (i.e., all clots) in the CTPA examination. While for "per patient" basis, it is not important for the CTPA-CAD to find all thrombi. Additionally, the CTPA-CAD responses can be evaluated on "first reader" or "second reader" basis. The "first reader" analysis, which is also called as "standalone performance," refers to the outcomes of the CTPA-CAD software in a defined dataset of clinical CTPA scans *without* interference of radiologists. The "second reader" performance means that the CTPA-CAD output is utilized to support the radiologist decision *after* he/she has assessed the examination primarily unassisted and uses the results of CTPA-CAD only to refine his/her judgment.

As explained in Section 3.4, in current clinical CTPA practice, the diagnosis of PE is divided in a yes-or-no decision, regardless to the colts' number, location, and severity of emboli [4]. It is, therefore, less important that a CTPA-CAD system finds all emboli in a CTPA scan. More significant tasks of CTPA-CAD seem to be: to increase the radiologist's certainty to rule in or out PE (i.e., improve sensitivity and specificity), to reduce the CTPA interpretation time, and to decrease inter-reader variability [2, 3]. Thus, most researchers prefer the "per patient" basis to evaluate the performance of CTPA-CAD because it is more clinically relevant than the "per clot" basis.

4.2. CTPA-CAD performance

The first study on a CTPA-CAD algorithm was published in 2002 by Masutani et al. [32] for a group of 19 high-quality CTPA examinations; they reported a sensitivity on a *per clot* basis of 100% with 7.7 false-positive findings per examination. Since then, numerous methods, utilizing various image analysis concepts, have been tested by different vendors and image analysis groups. Some CTPA-CAD algorithms have attained clinical merit, while some are still under development. This section reviews the performance of these methods, dividing them into two

groups. The first group describes the marketable CTPA-CAD available from famous vendors such as SIEMENS, PHILIPS, and GE. The second group describes underconstruction CTPA-CAD software. In general, the review focuses on the main image analysis aspects implemented in the CAD algorithm (if it was disclosed), the method's performance, size of dataset, and the characteristics of CTPA images, particularly the slice thickness that has direct impact on diagnosing PE.

4.2.1. Commercial CTPA-CAD

These are the CTPA-CAD methods that were developed at famous medical imaging vendors, for example, Philips (Philips Healthcare, Best, The Netherlands), Siemens (Siemens Medical Solutions, Germany), and GE (General Electric Healthcare, USA). They have been FDA approved and tested in a clinical environment. Since they are offered in the medical imaging market, the methodology (i.e., sequence of image analysis aspects) is not disclosed. This subsection presents the reports explaining their clinical performance "first reader" or "second reader" basis.

For CTPA-CAD made by *Philips*, two clinical trials by Wittenberg et al. [33, 34] and one by Lahiji et al. [35] were reported. The first trial by Wittenberg et al. was in 2010; they tested the CAD output on 225 negative and 67 positive CTPA scans (292 retrospective scans) acquired from 16 and 64 MDCT devices with 0.9 or 1 mm slice thickness [33]. For "first reader" basis, the results showed 94 and 21% sensitivity and specificity, in turn. The rate of FP stimuli was 4.7 per examination. The NPV was 92% indicating possibility to serve as reassurance for less experienced readers. The CAD also found seven FN scans, two at segmental and five at subsegmental vessels. The second trial was published in 2012 [34]. They examined the performance of six radiologists with and without the CTPA-CAD on 158 negative and 51 positive retrospective CTPA scans, which were obtained from 16 and 64 MDCT devices with 0.9 or 1 mm slice thickness. For "second reader" basis, there was no significant change in specificity, but the sensitivity increased in the range from 12% (expert reader) to 12 (radiologist-in-training or less expert). The rate of FP was 4.9 per scan. Lahiji et al., in 2014 [35], evaluated 26 negative and 40 positive CTPA scans from 256 MDCT device with 0.9 mm slice thickness. Although their study was to compare two different CTPA image reconstruction algorithms (the iterative and filtered back projection techniques), a CTPA-CAD software was used for the assessment. For "first reader" basis, the reported sensitivity and specificity for both image reconstruction techniques were in the range 85–97.2 and 26.9–61.5, respectively. The rate of FP was in the range 1.5–3.6.

For CTPA-CAD made by *Siemens*, Lee et al. studied 16 negative and 21 positive CTPA scans acquired from dual energy CT angiography (DCTA) with 1.2 mm slice thickness [36]. When both readers used the CAD prototype, the sensitivity was improved by approximately of 5% without significant loss in specificity. The rate of FP was 3.5 per examination. Blockmon et al. evaluated 79 CTPA scans (36 positive and 43 negative) from 16 and 64 CTPA devices at 1 mm slice thickness [37]. The radiologists, without the aid of CTPA-CAD, scored 84.4 and 92.6 sensitivity and specificity, in turn. For "first reader" basis, the CTPA-CAD achieved 93.8% sensitivity and 14.9% specificity; while it achieved 92.2% and 88.3% for "second reader" basis. The FP rate was 3.5 per scan. Earlier study was by Engelke et al. in 2008 [38]. They studied 56 positive CTPA scans obtained from 64 MDCT device with 0.6-mm slice thickness. On "second reader" basis, the four readers reported no significant loss of specificity while sensitivity increased in the range 3–7%. The FP rate was 4.1 per scan.

Wittenberg et al. compared the performance of three different CTPA-CAD systems made by *Philips*, *GE*, and *Siemens* [39]. They studied three groups of CTPA scans from 64 MDCT devices made in Philips, GE, and Siemens with 0.6, 0.9, and 1.5 mm slice thickness, in order. The three groups of dataset contained 38, 39, and 38 positive CTPA scans; it also contained 40, 40, 37 negative CTPA scans, respectively, according to each CTPA group. For "first reader" basis, the comparison yielded a sensitivity of 100, 97, and 92, specificity of 18, 15, and 13, and FP rate of 4.5, 6.2, and 3.7, respectively, to each group.

Table 2 summarizes the results of previous trials of different CTPA-CAD systems from different vendors. For comparison, the table also includes the results from PIOPED II (the largest clinical trial) explained in Section 3.4.2. The table illustrates the CTPA clinical performance once CTPA images are interpreted by the radiologist, the CTPA-CAD software (CAD first Reader basis), consensus between radiologist and the CTPA-CAD software (CAD second reader basis). The table consists of 7 main columns. The first column shows the author with the reference number. The second column indicates the interpretation procedure type (radiologist, the CTPA-CAD software, consensus of Radiologist and the CTPA-CAD software). The third column demonstrates the dataset's size indicating the number of positive and negative CTPA scans. The fourth, fifth, and sixth column indicate the performance in term of sensitivity, specificity and rate of FP, in order. Finally, the last column shows slice thickness used to acquire CTPA image. **Table 3** shows the range values of the sensitivity, specificity, and FP rate for each diagnosis protocol, which are reported in **Table 2**.

The findings listed in **Tables 2** and **3** indicate the following:

1. If CTPA scan is interpreted by radiologist only, the sensitivity and specificity may not reach 100%. The sensitivity range from 77.7% (for radiologist-in-training or less experience) to 94% (expert radiologist). While the specificity varies in the range 89–98% indicating almost perfect performance in excluding PE. The 100% specificity reported by Lee et al. [36] (**Table 2**) was reported on small number of negative CTPA scans, so it cannot be generalized.

2. For CTPA-CAD "first reader" basis, the marketable CTPA-CAD methods can score reliable high sensitivity, which can exceed the performance of an expert radiologist. However, the specificity is low (~20% in all reports in **Table 2**) due to 3.4–4.9 FP stimuli per CTPA scan. The 61.5 specificity reported by Lahiji et al. [35] is concluded from applying iterative reconstruction that is under research.

3. For CTPA-CAD "second reader" basis, the CAD can improve radiologists' sensitivity up to 7%. This increment in sensitivity coincides with no significant change in specificity. This enhancement can be substantial for inexperienced radiologist as reported by Wittenberg et al. [34], which one of the radiologists scored 90% with the aid of CTPA-CAD in comparison to 78% without the CAD assistance.

4. The results were obtained on different MDCT devices, thus the performance of CTPA-CAD is independent of scanner type. However, it is relevant to image quality and scanning protocols such as slice thickness. Actually, the slice thickness has significant impact on PE diagnosis. For example, Jung et al. [40] analyzed 15 positive and 25 negative CTPA scans acquired with slice thicknesses of 0.625, 1.3, and 2.5 mm from 64 MDCT device. As

Author	CTPA interpretation protocol	Dataset size		Sensitivity (%)	Specificity (%)	FP rate per scan	Slice thickness (mm), MDCT device
		Positive CTPA	Negative CTPA				
PIOPED II [10]	Radiologists	192	632	83	96	Not applicable	1.25 4, 8, 16 rows MDCT
Wittenberg [34]		51	158	78–94	89–98		0.9–1.0 16, 64 rows MDCT
Lee [36]		21	16	90.9	93.3–100		1.2 DCTA
Blackmoon [37]		36	43	84.4	92.6		1.0 16, 64 rows MDCT
Engelke [38]		56	—	77–93	—		0.6 64 rows MDCT
Wittenberg [33]	CTPA-CAD *Philips*, Siemens, or GE	67	225	94	21	4.7	0.9–1.0 16, 64 rows MDCT
Lahiji [35]		40	26	85–97.5	26.9–61.5	1.5–3.6	0.9 256 rows MDCT
Blackmoon [37]		36	43	93.8	14.9	3.5	1.0 16, 64 rows MDCT
Wittenberg [39]		38	40	100	18	4.5	0.6 64 rows MDCT
Wittenberg [39]		39	40	97	15	6.2	0.9 64 rows MDCT
Wittenberg [39]		38	37	92	13	3.7	1.5 64 rows MDCT
Wittenberg [34]	Consensus between Radiologist and CTPA-CAD	51	158	90–96	91–98	4.9	0.9–1 16, 64 MDCT
Lee [36]		21	16	95.5	93.3–100	3.5	1.2 DCTA
Blackmoon [37]		36	43	92.2	88.3	3.5	1.0 16, 64 rows MDCT
Engelke [38]		56	—	84–96	—	4.1	0.6 64 rows MDCT

Table 2. "Per patient" CTPA interpretation by the radiologist, "first reader" marketable CTPA-CAD software, and "second reader" CTPA-CAD software, showing sensitivity, specificity, rate of FP responses, and the characteristics of dataset used in the clinical trials.

CTPA interpretation protocol	Sensitivity (%)	Specificity (%)	FP rate per scan
Radiologists	77–94	89–98	—
CAD (Philips, Siemens, or GE)	85–100	13–61.5	1.5–6.2
Consensus between radiologist and CAD (Philips, Siemens, GE)	84–96	88.3–100	3.5–4.9

Table 3. "Per patient" range of the values of sensitivity, specificity, rate of FP responses, based on each protocol of CTPA interpretation.

slice thickness increases, there was significant decrease of PE diagnosis of lobar, segmental, subsegmental clots on both the axial and coronal CTPA views. They concluded that a slice thickness of 1 mm is a must to achieve high sensitivity, particularly the subsegmental PE. This impact is applicable to CTPA-CAD and must be considered in any CAD prototype [2, 3]. This matter, among other variables, is further described in Section 4.3.

Consequently, the marketable CTPA-CAD software can increase reader sensitivity for the detection of PE, particularly the segmental and subsegmental pulmonary clots, and enforce reader confidence for the diagnosis of PE without significant loss of specificity. This rise in sensitivity means less FN CTPA scans (Eq. (1)), thus improving patient health.

4.2.2. Underconstruction CTPA-CAD

There are nonmarketable CAD systems under construction by researchers. They share the employment of CTPA pulmonary vessels segmentation, candidate clot detection, and texture and feature computation with/without morphology analysis on 2D and 3D levels. However, they explored recent advances in computer sciences to reduce the FP rate such as complex mathematical classifier [41–43] and artificial intelligence (e.g., neural networks) [44, 45]. Thus, they reported their results on "per clot" basis.

The results in **Table 4** demonstrate that the "per clot" CTPA-CAD's sensitivity is in the range from 63–80%. This qualifies those CAD prototypes to be tested on "per patient" basis. However, the rate of FP stimuli is still high, so a low specificity value, as those in **Table 2**, is again very likely to happen. False-positive stimuli are the main burden hindering radiologist from accepting the

Author	Number of clots in CTPA cases	Sensitivity (%)	FP rate per scan
Bouma [41]	318 in 57 positive CTPA	63	4.9
Zhou [42]	595 in 59 positive CTPA	80	22.6
Zhou [43]	537 in 50 positive CTPA (PIOPED II)	80	8.6
Park [44]	44 in 18 positive CTPA	63.2	18.4
Tajbakhsh [45]	326 in 121 positive CTPA	83	2

Table 4. "Per clot" sensitivity and FP rate for underconstruction CTPA-CAD prototypes.

superfluous sensitivity of CTPA-CAD. To reduce the FP rate, Tajbakhsh [45] employed 3D presentation of PE and blood vessels, coupled to neural network, to produce 2 FP per CTPA scan (**Table 4**). Al-hinnawi et al. [46] suggested another 3D technique, but simpler than neural networks that requires training and calibration on dataset characteristics, to reduce the FP rate. In the final step of their CTPA-CAD system, the stimuli from three CTPA views were orthogonally recombined to produce a single *interactive 3D display of PE candidates* from the CTPA case, as illustrated in **Figure 7**. Thus, this would permit, in a single analysis instead of slice by slice analysis, the assessment of CAD performance on the aggregated CAD responses on the three CTPA views of each patient. This could reduce time, and consequently reduce burden to radiologist. Clots that are bigger in size than 1 mm^3 were retained based on the voxel size of the CTPA scan. Thus, the CAD system can be tuned in accordance with the variations in CTPA acquisition settings due to patient differences, which was not employed in previous marketable CTPA-CAD systems or underconstruction CTPA-CAD prototypes. This reduces the variations in CAD outputs due to variation in patient preparation such as slice thickness. They reported that this approach would reduce the FP rate of from CAD systems, such as those in **Tables 2** and **4**, by 30% while it increases or ascertains the correct rate of CTPA-CAD's TP stimuli as much as 27%.

4.3. Factors affecting CTPA-CAD performance

CTPA-CAD systems are image quality dependent [2, 3, 47, 48]. As for any X-ray imaging technique, the CTPA image quality is ruled by factors related to subject variance, acquisition parameters, patient preparation, and dose management [4, 49]. The subject variances such as
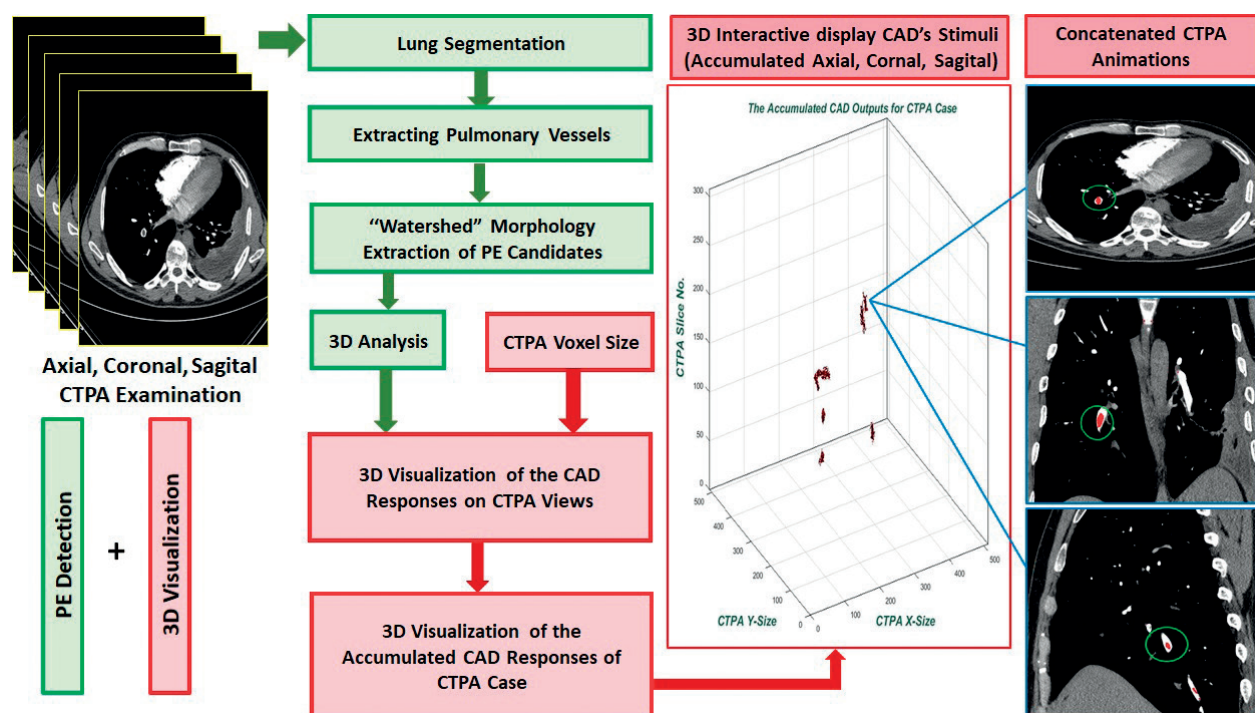

Figure 7. Three dimensional visualization of CTPA-CAD output (courtesy from radiological physics and technology no. JSMP30–180024).

age, sex, race, presence of risk factors, prevalence and morphology of the clots, they do *not* have impact on CTPA image quality; so they should not influence the CTPA-CAD outcome. Thus, there is no need to calibrate the CAD system based on different patients or countries.

However, the acquisition and patient preparation variables are fundamental factors in CTPA image quality. They may lead to bias in the CTPA-CAD output [2, 3, 47–49]. Acquisition parameters include KV, mA, type of reconstruction algorithm, accurate MDCT window, and any post processing filtration, among other technical parameters, they all affect CTPA image contrast. On the other hand, patient preparation include mainly the slice thickness, correct contrast agent dose and rate of injection, and accurate timing to acquire CTPA images during the pulmonary vessels are filled with contrast agent not after it drained to heart, they all affect the precise depiction of clots with variable sizes and locations [4, 7, 10, 40]. While radiologist, and the clinical physicist or radiographer, may be relatively unaware to such factors, it is believed for sure that they have direct impact on CAD systems because they lead to alterations in the representation of radiographic features on which CAD relies [2, 3, 48, 50].

Dose management also has crucial role on any CAD output. As reducing X-ray dose is main concern in imaging, different vendors provide imaging protocols and reconstruction techniques to reduce patient dose without substantially risking the image quality. These ultra-low dose, or even low dose, settings lead to lower contrast to noise ratio, which in turn leads to higher possibility to CT artifacts and lower capability to spot diseases [51–53]. These parameters are relevant to any CAD system [2, 3, 47, 48], so can greatly affect the PE CAD performance.

4.4. CTPA-CAD recommendations

Therefore, subsequently to the discussion mentioned earlier, the CTPA-CAD manufactures should clearly describe the operating characteristics of their PE CAD prototypes. This include, the supported range of equipment, CTPA image acquisition settings, patient preparation requirements, reconstruction algorithms, and patient special cases such as those with additional lung defects, among other relevant factors, that radiologist need to be aware during the use of CTPA-CAD. Additionally, in case of CTPA-CAD comparison with findings from previous CTPA scans is used to assess decisions on diagnosis, disease progression, and/or treatment effectiveness, care must be considered to match the acquisition conditions accordingly to CTPA-CAD operating manual [2, 3, 47–53].

4.5. Summary

This section described the current status of utilizing PE CAD prototypes in CTPA clinic. The necessity of CAD systems in PE diagnosis is highlighted, and different possible CAD group of outputs are explained. Then, according to research centers from different countries, the performance of marketable and underdevelopment CTPA-CAD systems is elucidated. The PE CAD performance can be described according to "per clot" or "per patient" basis, and "first reader" or "second reader" basis. The "per patient" basis is more relevant to CTPA clinical practice than "per clot". Both the "first reader" and "second reader" basis lead to high sensitivity that can reach 100%, outweighing the radiologist performance. However, the

specificity drops dramatically and become much less than the radiologist performance in case of "first reader" basis. Studies showed that the best operating scenario is the "second reader" basis because it improves sensitivity, which means less FN results, while it guarantees no significant change in specificity, in comparison to human observer performance. The factors affecting the CTPA-CAD output were described at the end of this section, this yielded to suggest recommendation.

5. Conclusion

This chapter presents comprehensive *current status* knowledge in the PE angiography clinic. The clinical proofs of thrombosis are explained in Section 2. Knowledge of PE epidemiology, predisposing factors, pathophysiology, classifications, diagnostic medical imaging modalities, and treatments procedures are described. Then, in Section 3, concentration is focused on describing the CTPA technology that is the clinically accepted as the best first-line imaging procedure in PE diagnosis because it is fast, lowest invasive, and the highest sensitivity procedure, among other medical imaging modalities. Issues covered are CTPA physics, technology, examination, radiographic appearance, and PE features, the clinical trials in term of sensitivity, specificity, PPV, and NPV, are explained. Section 4 provides demonstration of the art of CAD system and their influence on improving the PE diagnoses by being eligible to reduce miss diagnosis by radiologist. Advantages and disadvantages of assessing CTPA-CAD performance with regard to "per patient", "per clot", "first reader", and "second reader" basis are explained. Results suggested that the "second reader" along with "per patient" basis is the best scenario to utilize PE CAD systems, because this raises the sensitivity without effect on specificity of radiologist performance. Precautions and recommendations of optimal practice of PE CAD prototypes are described indicating the necessity to follow the operation manual specifications, particularly the CTPA acquisition parameters and patient preparation, which the CAD relies on.

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