CT angiography in the diagnosis of cardiovascular disease: a transformation in cardiovascular CT practice

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Abstract: Computed tomography (CT) angiography represents the most important technical development in CT imaging and it has challenged invasive angiography in the diagnostic evaluation of cardiovascular abnormalities. Over the last decades, technological evolution in CT imaging has enabled CT angiography to become a first-line imaging modality in the diagnosis of cardiovascular disease. This review provides an overview of the diagnostic applications of CT angiography (CTA) in cardiovascular disease, with a focus on selected clinical challenges in some common cardiovascular abnormalities, which include abdominal aortic aneurysm (AAA), aortic dissection, pulmonary embolism (PE) and coronary artery disease. An evidence-based review is conducted to demonstrate how CT angiography has changed our approach in the diagnosis and management of cardiovascular disease. Radiation dose reduction strategies are also discussed to show how CT angiography can be performed in a low-dose protocol in the current clinical practice.

Keywords: Cardiovascular disease; computed tomography angiography (CTA); diagnosis; visualisation

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Introduction

Over the last two decades, cardiac computed tomography (CT) has witnessed significant developments in the diagnosis of cardiovascular disease, owing to the technical improvements in CT imaging, which allows rapid data acquisition with high spatial resolution. CT angiography (CTA) has been widely used in the diagnostic evaluation of many cardiovascular diseases, and this technique currently serves as the first line modality in the early diagnosis of abdominal aortic aneurysm (AAA), aortic dissection and pulmonary embolism (PE) (1-5). Coronary CT angiography (CCTA) represents one of the most important technical advancements in cardiovascular CT practice, and it is becoming a standard clinical assessment for patients with low to intermediate pre-test probability for coronary artery disease (6-15). CTA is also commonly used to follow-up patients treated with endovascular stents and stent grafts with the aim of determining stent and stent graft patency, stent graft-related complications (16-20).

Despite significant improvements in cardiovascular CT practice, CTA still remains a challenging procedure in routine clinical practice due to the following reasons: first, acquisition of optimal image quality remains an issue in CCTA, as heart rate control with appropriate electrocardiogram (ECG)-gating and good time of contrast injection comprises an essential component of CTA. Second, radiation dose associated with CTA is a medical concern; although significant progress has been made in reducing radiation dose with the use of dose-saving strategies, with resultant dose value similar to or even lower than invasive coronary angiography (21). However, a collaborative team between skilled medical imaging technologists and physicians play an important role in achieving such a low-dose protocol with diagnostic quality images, since
suboptimal scanning techniques or inappropriate referral protocols result in suboptimal image quality and high radiation dose.

This review provides an overview of the diagnostic application of CTA in cardiovascular CT practice with a focus on the diagnostic accuracy of CTA in the common cardiovascular disease, including AAA, aortic dissection and PE. CTA in the assessment of endovascular stent graft repair of aortic aneurysm and aortic dissection is also reviewed. More attention is paid to the CCTA in the diagnosis of coronary artery disease with regard to the diagnostic and prognostic value of this rapidly evolved technique. Finally, recently introduced capabilities for CCTA such as fractional flow reserve (FFR) CT and effective dose reduction through iterative reconstruction (IR) are highlighted.

**CTA in AAA and endovascular stent graft repair**

With rapid technically developments in CT imaging technique, in particular, the widespread use of multislice CT, CTA has become a routine imaging modality in the diagnostic evaluation of patients with AAA, while invasive angiography is only reserved for solving complications situations where CTA shows indeterminate results.

CTA imaging of abdominal aorta, aneurysm and relationship between the aneurysm and aortic branches has been complemented by a number of two-dimensional (2D) and 3D reconstruction visualisations which enhances the diagnostic value of CTA to a greater extent (22-27). In addition to the routinely viewed 2D axial images (Figure 1A), multiplanar reformation (MPR) CTA images are generated for measurement of aneurysm length in relation to the proximal and distal aneurysm necks (Figure 1B), while maximum-intensity projection (MIP) is commonly used to demonstrate the extent of aneurysm in relation to the aortic branches (Figure 1C). 3D volume rendering technique (VRT) provides volumetric information of the aneurysm and other structures as shown in Figure 2. Measurement of proximal aneurysm neck length between the renal arteries and aneurysm plays an important role in pre-operative planning.
While open surgical repair of AAA is still commonly performed, EVAR has been increasingly used in many clinical centres due to its less invasiveness, lower procedure-related complications compared to open surgery (28-30). EVAR has been reported to be especially suitable for patients with co-morbid medical conditions such as cardiac disease, chronic obstructive pulmonary disease, diabetes, renal disease, cerebrovascular disease or peripheral artery disease (31,32). Stent-graft integrity is of paramount importance to EVAR of AAA, and this can only be assessed by medical imaging.

Currently, CTA is the preferred imaging modality for routine imaging follow-up of postoperative EVAR (16-19). CTA follow-up of EVAR includes measurements of aneurysm diameter to determine aneurysm sac size change (33-35), detection of stent graft-related complications such as endoleaks (Figure 4), which is the most commonly
reported occurrence following EVAR (36-39), and stent graft migration (Figure 5) (40,41).

Another 3D visualisation tool generated from CTA is virtual intravascular endoscopy (VIE) which shows unique intraluminal views of the aortic wall as well as stent wires (42-45). Studies have shown that VIE allows demonstration of intraluminal appearances of stent grafts (Figure 6), in particular the relationship between stent wires and renal artery ostia (Figure 7). This is clinically significant as the long-term outcomes of EVAR still remains to be understood, thus, VIE serves as a complementary tool to conventional CTA-generated visualisations for accurate assessment of treatment outcomes of EVAR (42-46).

**CTA in aortic dissection**

CTA or echocardiography is usually performed in patients with suspected acute aortic dissection based on clinical presentation and initial investigations (47-50). A systematic review of the diagnostic value of CTA, transesophageal echocardiography, and magnetic resonance imaging (MRI) reported that the mean sensitivity and specificity was more than 95% for all three examinations (51). Although MRI was found to be slightly superior to the other two modalities in patients with high pretest probability of aortic dissection, CTA is the preferred imaging modality in patients with low or intermediate pretest probability of aortic dissection; in particular, CT is widely available in the emergency department (47).

CTA-generated axial CT imaging supplemented by 2D or 3D reconstructions is able to identify the intimal flap which separates the true lumen from the false lumen, the size of true and false lumen (Figure 8), localization of the
intimal tear, extent of aortic dissection with regard to the involvement of aortic branches (Figure 9), and the presence of hematoma, mediastinal hematoma or pleural effusion (52).

Conventional CTA without ECG-gating allows for acquisition of static images of intimal flap, thus reflects the configuration of the intimal flap at an arbitrary time point. However, motion artifacts of the ascending aorta or of an intimal flap can cause cardiac pulsation, thus affecting image quality in aortic dissection (53). ECG-gated CTA is therefore recommended for evaluation of aortic dissection as it allows the phase-resolved cine imaging by eliminating the impact of motion artifacts due to cardiac pulsation (54), and the 4D images enable assessment of the dynamics of the intimal flap movement during a cardiac cycle (55-57). Studies reported that ECG-gated CTA can assess the intimal flap motion by demonstrating the actual status of true and false lumen during cardiac cycle (Figure 10), thus, providing more information about true lumen collapse. Identification of pulsating and static types of aortic dissection with ECG-gated CTA is considered useful for differentiation of unstable aortic dissection from stable one (55,58).

The management of an aortic dissection depends on the type, time course, and symptoms associated with the dissection. Acute Stanford type A aortic dissection represents

Figure 8 Sagittal reformatted CT angiography shows Stanford type A aortic dissection with true lumen (short arrows) compressed by the false lumen. Aortic dissection arises from the ascending aorta as indicated by the large arrows. CT, computed tomography.

Figure 9 2D axial images of CT angiography show Stanford type A aortic dissection extending from the ascending aorta to the abdominal aorta with true lumen (short arrows) much smaller than the false lumen. The left renal artery (long arrow) arises from the true lumen. 2D, two-dimensional; CT, computed tomography.
a surgical emergency, and it is managed by surgical repair, while management of Stanford type B dissection is determined by the situation whether the dissection is complicated or not. Due to invasiveness and high mortality associated with surgical repair, endovascular stent grafting is increasingly used as a less invasive alternative to treat complicated type B dissection (59). CTA is used as a routine imaging modality for follow-up of endovascular repair of aortic dissection by showing the stent graft in relation to the aortic branches (Figure 11), stent grafts or stents position in the aorta (Figure 12), and volumetric changes in the true and false lumen (Figure 13) (60,61).

Figure 10 (A) Typical axial source images of a subject with aortic dissection in which true lumen (TL) becomes maximal at 20% of the R-to-R interval of the electrocardiogram (left) and TL becomes minimal at 80% of the R-to-R interval (right); (B) typical multiplanar reconstruction images from the left anterior oblique view of a subject with aortic dissection in which TL becomes maximal at 20% of the R-to-R interval of the electrocardiogram (left) and TL becomes minimal at 80% of the R-to-R interval (right). Reprint with permission from ref (55).

CTA in PE

CT pulmonary angiography (CTPA) has been widely recognized as the method of choice for diagnosis of suspected PE due to its superior sensitivity and specificity to ventilation-perfusion (V/Q) radioisotope scanning (62,63). The main advantages of CTPA over V/Q scans in PE include higher diagnostic accuracy, faster acquisition time with high contrast images, and readily availability at many clinical centres (64). The wide availability and high diagnostic performance have led to the increasing use of CTPA as the first line modality to detect or exclude PE.
Figure 11 A series of 2D axial images in a patient with Stanford type B aortic dissection treated with endovascular stent graft show that the stent graft is placed in the ascending aorta, just below the left subclavian artery. 2D, two-dimensional.

Figure 12 Adjunctive stent placement during the initial procedure. (A) The right renal artery originally perfused by the false lumen (left panel) was treated with a stent inserted from the true lumen through the uncovered dissection stent (right panel). This patient also underwent coil embolization of the distal false lumen and a lumbar artery; (B) the dissected right common iliac artery (left panel) was treated with placement of two stents (right panel). Reprint with permission from ref (60).
both in the emergency department and in-patient setting.

The use of CTPA as a reliable diagnostic imaging modality to exclude PE has been confirmed by clinical trials (65,66). A meta-analysis of safety of ruling out PE by CTPA showed that a normal CTPA alone can safely exclude PE in all patients in whom CTPA is required to rule out PE, with pooled 3-month venous thromboembolism rate for patients with a normal CTPA being 1.2% (95% confidence interval: 0.8-1.8%) (67).

Technical improvements in multislice CT allow accurate detection of PE, in particular subsegmental PE. A meta-analysis shows that the rate of isolated subsegmental PE detected by multislice CTPA is twice as high when compared to that used by single slice CTPA (68). Despite high radiation dose associated with CTPA, it still remains the most reliable imaging modality for detection of PE. The PIOPED III study reported that MR pulmonary angiography (MRPA) has a sensitivity of 78% and a specificity of 99% compared to CTPA and V/Q scans, which are regarded as the reference standard (69). Furthermore, MRPA was technically inadequate in 25% of the patients. Similar diagnostic value of MRPA was reported in another study with similar percentage of inconclusive results due to technical reasons (70).

For visualization of the pulmonary embolism with CTPA, 2D axial and multiplanar reformation images are the most commonly used visualization tools for detection of segmental and subsegmental PE (Figure 14). Others postprocessing tools are also available to evaluate the CTPA datasets, which include MIP, and VTR (71,72) (Figure 15).

**CCTA in coronary artery disease**

Increasing evidence shows that CCTA is a well-established imaging modality in the diagnosis of coronary artery disease due to its less invasiveness, high diagnostic value, and widespread accessibility (7-10,73-77). Expansion of multislice CT systems from a 64- to 320-slice system has allowed for the accurate assessment of stenosis severity and atherosclerotic plaque composition (Figure 16) (78), or even the acquisition of whole-heart coverage in one gantry rotation (15). Systematic reviews and meta-analyses reported the high diagnostic accuracy of 320-slice CCTA, with sensitivity similar to that observed in 64-slice CCTA, but specificity higher than in 64-slice CCTA (79,80). Although extended z-axis coverage is improved with use of 320-slice CCTA, temporal resolution of 320-slice CT is inferior to that of 64- or 128-slice CT, thus, heart rate control is still necessary in most of CCTA examinations (81). Table 1 summarizes the diagnostic value of these studies performed with 64- and 320-slice CCTA in coronary artery disease.

In addition to the excellent diagnostic performance in coronary artery disease, CCTA also shows high prognostic value in the prediction of major adverse cardiac events. A direct correlation between CCTA findings and the occurrence of future cardiac events has been reported by studies based on short-term to long-term follow-up, with results showing that normal CCTA is associated with a very
Figure 14 (A) 2D axial CT images show pulmonary embolism located in the main pulmonary trunk, with involvement of bilateral main pulmonary arteries (arrows); (B) the same patient as A, pulmonary embolism extends to the segmental branches (arrows). 2D, two-dimensional; CT, computed tomography.

A low rate of adverse cardiac events (<1%), while in patients with obstructive coronary artery disease, the event rate is significantly higher (3-59%) (82-91) (Figure 17). These results indicate that CCTA could serve as an independent predictor of major adverse cardiac events in patients with suspected coronary artery disease, although multicentre studies with long-term follow-up are required since most of the currently reports are based on single centres’ experience with short to mid-term follow-up.

In recent years, there has been an increasing interest in the investigation of diagnostic performance of non-invasive FFR derived from CCTA (FFRCT). Computation of FFRCT is performed by computational fluid dynamics (CFD) modelling after segmentation of coronary arteries and left ventricular myocardium. The FFRCT ratio is obtained by dividing the mean pressure distal to the coronary stenosis by the mean aortic pressure, which can be measured during CFD simulations. An FFR of ≤0.80 is currently used as a cut off value to determine coronary stenoses responsible for ischemia (Figures 18,19) (92,93).
Figure 15 CT pulmonary angiography in a 57-year-old man with mild pleuritic chest pain. (A) Consecutive transverse sections show isolated peripheral pulmonary embolus (arrows) in a subsegmental pulmonary artery in segment 9 of the left lung; (B) oblique sagittal multiplanar reformation also shows embolus (arrow); (C) coronal volume-rendered display (posterior view) shows isolated peripheral filling defect (arrow) in otherwise normal pulmonary vascular tree. Reprint with permission from ref (72). CT, computed tomography.

Figure 16 Coronary CT angiography characterization of plaque composition. (A) A calcified plaque (arrow) is seen in the proximal segment of right coronary artery in a 65-year-old woman with suspected coronary artery disease; (B) a non-calcified plaque (arrow) is detected in the proximal segment of right coronary artery in a 67-year-old woman with known coronary artery disease; (C) a mixed plaque (arrow) is observed in the proximal segment of left anterior descending coronary artery in a 55-year-old female with suspected coronary artery disease. CT, computed tomography.
Figure 17 Unadjusted all-cause 3-year Kaplan-Meier survival by presence, extent, and severity of coronary artery disease by coronary CT angiography as stratified by age <65 or ≥65 years. Although rates of mortality in relationship coronary artery disease extent are lower in patients age <65 years (A), patients age <65 years with 2- and 3-vessel coronary artery disease experience a higher relative rate of mortality referenced to patients age <65 years with no coronary artery disease in comparison with patients age ≥65 years with 2- and 3-vessel coronary artery disease referenced to patients age ≥65 years with no coronary artery disease (B). Reprint with permission from ref (91). CT, computed tomography.

Currently, there are three multicentre trials, namely DISCOVER-FLOW (Diagnosis of Ischemia-Causing Coronary Stenoses by Noninvasive FFR Computed from Coronary Computed Tomographic Angiograms, conducted at four sites in three countries including Korea, Latvia and USA), DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography, conducted at 17 centres in 5 countries including Belgium, Canada, Korea, Latvia and USA) and NXT (NeXt sTeps, conducted at 10 centres in 7 countries including Australia, Denmark, Germany, Japan, Korea, Latvia and the UK) investigating the diagnostic value of FFRCT in coronary artery disease (94-96). On a per-patient analysis, diagnostic sensitivity and specificity of FFRCT ranged from 86-90% and 54-79%, while on a per-vessel analysis, diagnostic sensitivity and specificity of FFRCT were 84% and 86-

### Table 1 Diagnostic value of coronary CT angiography in coronary artery disease according to systematic reviews and meta-analyses

<table>
<thead>
<tr>
<th>Type of CT scan</th>
<th>First author</th>
<th>No. of articles in the analysis</th>
<th>Patient-based sensitivity % [95% CI]</th>
<th>Patient-based specificity % [95% CI]</th>
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<td>64-slice coronary CT angiography</td>
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<td>89 [83-94]</td>
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<td>88 [79-97]</td>
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<td>Guo et al. 2011 (14)</td>
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<td>98 [99-99]</td>
<td>87 [83-90]</td>
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<td></td>
<td>Salavati et al. 2012 (73)</td>
<td>25</td>
<td>99 [97-99]</td>
<td>89 [84-92]</td>
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<td>Prospectively ECG-triggered coronary CT angiography</td>
<td>Von Ballmoos et al. 2011 (74)</td>
<td>16</td>
<td>100 [98-100]</td>
<td>89 [82-89]</td>
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<tr>
<td></td>
<td>Sun et al. 2012 (75)</td>
<td>14</td>
<td>99 [98-100]</td>
<td>91 [88-94]</td>
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<td></td>
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<td>22</td>
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<td>92.1 [87.2-97]</td>
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<td>320-slice coronary CT angiography</td>
<td>Gaudio et al. 2013 (79)</td>
<td>7</td>
<td>95.4 [88.8-98.2]</td>
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<td>Li et al. 2013 (80)</td>
<td>10</td>
<td>93 [91-95]</td>
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CT, computed tomography; ECG, electrocardiogram.

Figure 17 Unadjusted all-cause 3-year Kaplan-Meier survival by presence, extent, and severity of coronary artery disease by coronary CT angiography as stratified by age <65 or ≥65 years. Although rates of mortality in relationship coronary artery disease extent are lower in patients age <65 years (A), patients age <65 years with 2- and 3-vessel coronary artery disease experience a higher relative rate of mortality referenced to patients age <65 years with no coronary artery disease in comparison with patients age ≥65 years with 2- and 3-vessel coronary artery disease referenced to patients age ≥65 years with no coronary artery disease (B). Reprint with permission from ref (91). CT, computed tomography.
Figure 18 Fractional flow reserve (FFR) derived from computed tomography (CT) angiography (FFR<sub>CT</sub>) results for 66-year-old man with multivessel coronary artery disease but no lesion-specific ischemia. (A) Coronary computed tomography angiography (CCTA) demonstrating stenosis in the left anterior descending coronary artery (LAD); (B) FFR<sub>CT</sub> demonstrates no ischemia in the LAD, with a computed value of 0.91; (C) invasive coronary angiography (ICA) with FFR also demonstrates no ischemia in the LAD, with a measured value of 0.89; (D) CCTA demonstrating stenosis in the left circumflex coronary (LCx) artery; (E) FFR<sub>CT</sub> demonstrates no ischemia in the LCx, with a computed value of 0.91; (F) ICA with FFR also demonstrates no ischemia in the LCx, with a measured value of 0.91. Reprint with permission from ref (92).

Figure 19 FFR<sub>CT</sub> results for 66-year-old man with multivessel coronary artery disease and lesion-specific ischemia. (A) Coronary CT angiography (CCTA) demonstrating stenosis in the left anterior descending coronary artery (LAD); (B) FFR<sub>CT</sub> demonstrates ischemia in the LAD, with a computed value of 0.64; (C) invasive coronary angiography (ICA) with FFR also demonstrates ischemia in the LAD, with a measured value of 0.72; (D) CCTA demonstrating stenosis in the left circumflex (LCx); (E) FFR<sub>CT</sub> demonstrates ischemia in the LCx, with a computed value of 0.61; (F) ICA with FFR also demonstrates ischemia in the LCx, with a measured value of 0.52. Reprint with permission from ref (92). FFR<sub>CT</sub>, fractional flow reserve (FFR) derived from coronary computed tomography (CT) angiography.
88%, respectively. The present findings support that FFRCT is superior to CCTA for the diagnosis of ischemia-causing lesions on both per-patient and per-vessel analysis as determined by an invasive FFR the reference standard. However, more multicentre trials need to be performed to compare the clinical impact of FFRCT guided versus standard diagnostic evaluation on clinical outcomes, costs and quality of life in patients with suspected coronary artery disease.

**CTA-radiation dose**

It is a well-known fact that CT is associated with high radiation dose which has raised concerns in the medical field over the last decade. With increasing applications of CTA in the cardiovascular practice, the research focus has shifted from the previous emphasis on diagnostic value of CTA to the current focus on reduction of radiation dose with acceptable diagnostic image quality. This is reflected by implementing various dose-reduction strategies with effective outcomes having been achieved.

CTA is commonly used as the gold standard of surveillance in patients following EVAR of AAA. However, excessive dependence on CT is expensive and exposes the patients to nephrotoxic intravenous contrast and ionizing radiation (97,98). Increasing the proportional use of non-nephrotoxic imaging modalities after EVAR has been advocated as an alternative approach to reduce surveillance-related morbidity (99). On the basis of 5-year follow-up outcomes, Sternbergh et al. proposed a modified surveillance protocol to alter the intensity and frequency of postoperative imaging follow-up. In patients without early endoleaks, the 6-month surveillance is eliminated, and the yearly aortic ultrasound examination is recommended for long-term surveillance of more than 1 year (100). There is increasing evidence of a trend from using conventional CT follow-up to ultrasound monitoring (100,101), so there is a need for a contemporary evaluation of surveillance after EVAR. A survey involving 41 clinical centres experienced in EVAR in the UK has shown there is significant heterogeneity in national practice for postoperative surveillance after EVAR (102). Intensive use of CT was observed in some centres and this may lead to cumulative renal injury due to repeated administration of contrast agents and radiation exposure. A recent study concluded that contrast-enhanced ultrasound is as accurate as CTA in monitoring endoleaks, aneurysm sac diameters, and target vessel patency in patients treated with fenestrated stent grafts (103).

The increased use of CTPA, especially in young patients with suspected PE raises concerns about the risk of radiation-induced malignancy and developing contrast-induced nephrotoxicity. Low radiation dose CTPA protocols with low contrast volume are increasingly studied due to the advantages of reducing radiation dose and minimising the risk of contrast-induced nephropathy (104-108). Low tube voltage and high pitch protocols have been reported to be effective approaches for reduction of radiation dose and contrast volume during CTPA examinations. Studies reported that using 80 kVp in CTPA can reduce radiation dose by 40% and contrast volume by 25% without compromising image quality (109,110). IR is a recently introduced algorithm which has been shown to reduce image noise and improve image quality while significantly reducing radiation dose in CT scans (111-113). High-pitch CTPA with low kVp combined with IR has been reported in recent studies to show that radiation dose is reduced by 52%, with contrast volume of 20 mL used in low-dose protocol (114,115). Another strategy on dose reduction is the application of dual-energy CT (DECT) which allows material decomposition of soft tissue, iodine and air within the chest CT scan. DECT has been shown to reduce patient dose by 28% compared with single-source CT while improving image visualisation of pulmonary vessels and diagnostic confidence (116,117). Further studies will provide more evidence of the clinical impact of DECT on CTPA (118).

High radiation dose associated with CCTA is well recognised in the literature, with significant progress having been made over the last decade on dose reduction during CCTA examinations. The commonly used dose-reduction strategies include ECG-controlled tube current modulation, adjustment of kVp values based on patient’s body mass index, high-pitch CCTA protocols, prospectively ECG-triggered CCTA, and use of IR algorithms (74-77,119-128). With use of these approaches, radiation dose can be reduced by more than 80% from initially 20 mSv to about 2 mSv while still maintaining high level of diagnostic accuracy. Currently, the low-dose CCTA protocols are increasingly used in clinical practice with dose similar to or even lower than of invasive coronary angiography. Dose of less than 1 mSv are already achievable with the current CT scanners, while ultra-low-dose CCTA has been reported in a recent study with the mean radiation dose of 0.29 mSv, which is comparable to a chest x-ray examination in two views (Figure 20) (129). These technical developments confirm that this technique has become a more attractive alternative to...
invasive coronary angiography.

**Summary and concluding remarks**

CT angiography represents the most important development in CT imaging, and it has evolved from the initial role of serving as a supplementary modality to an essential tool that plays an important role in the diagnosis and management of cardiovascular disease which involves arterial system in the body. Technological advancements in CT data acquisition and image processing techniques have enabled this technique to become a routine imaging modality in daily clinical practice. With emergence of novel CT scanner geometries, advanced data reconstruction and postprocessing techniques, CT angiography will continue to play a dominant role in the diagnosis of cardiovascular disease which involves arterial system in the body.
disease, prediction of disease extent and assistance of clinicians in effective patient management.

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