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Review Article

Advances in myocardial CT perfusion imaging technology

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Abstract: With the booming development of CT technology, CT-based myocardial perfusion imaging (CTP) has begun to mature and has exhibited great advantages and application prospects as a complete evaluation method of anatomy and function for CAD. This article summarizes the CTP technology progress and analytical methods of CTP in recent years, briefly reviews the clinical relevance, and subsequently discusses the limitation and future development.

Keywords: Coronary artery disease, tomography, X-ray computed, myocardial perfusion imaging, myocardial ischemia

Introduction

Computed tomography angiography (CTA) has already been demonstrated to be one of the most safe and reliable technologies for detecting and excluding severe obstructive coronary artery disease (CAD) [1, 2]. However, such diagnoses are limited to the anatomical level and have a tendency to overestimate the degree of stenosis [3]. In contrast, the myocardial perfusion imaging (MPI) technique has more advantages in diagnosing and evaluating myocardial perfusion defects. Traditional MPI techniques mainly include single photon-emission CT myocardial perfusion imaging (SPECT-MPI) and cardiac magnetic resonance myocardial perfusion imaging (CMR-MPI). Nevertheless, in the past few years, with the rapid development of multislice CT technology and continuous development of image post-processing and reconstruction techniques, the temporal and spatial resolution have greatly improved, and the coverage of the Z-axis has increased. CT-based myocardial perfusion imaging (CTP) has aroused extensive concern and recognition for evaluating the anatomy and physiology of myocardial ischemia related diseases in one station [4-6]. This article will review the technical progress, limitations, and developing future directions of CTP.

Physiological fundamentals of perfusion imaging

In the coronary artery system of a healthy body, the pressure gradients within the artery lumen are relatively constant. When coronary obstructive stenosis occurs, additional resistance arises. Consequently, the pressure distal to the stenosis decreases, which reduces the effective perfusion pressure and the blood flow in the corresponding distal portion of the blood vessels. Normally, under a certain range of perfusion pressures, the self-adjusting mechanism of the vasculature can maintain the blood flow at a relatively constant level during rest conditions. However, the myocardial blood flow (MBF) begins to decrease in cases with more than 50% luminal stenosis [7, 8]. If the luminal stenosis exceeds 85% during resting conditions or hyperemia is induced by exercise or pharmacologic stress, the reduction in hyperemic flow exceeds 50% [9, 10], which consequently leads to a decrease in myocardial perfusion and its related symptoms.

Traditional MPI techniques

Traditional MPI techniques primarily include SPECT-MPI and CMR-MPI, and both methods can detect the myocardial perfusion defects

Table 1. Comparisons of PET/SPECT-MPI, MR-MPI and CTP

	Advantages	Limitations
PET/SPECT-MPI	High sensibility and diagnosis accuracy	Low temporal resolution
		Poor sensitivity for tiny ischemia
		Misalignment artifacts
		Misalignment artifacts
MR-MPI	Free of ionizing radiation	Long examination time
	High soft tissue contrast than CTP and PET/SPECT	Lots of contraindications
		Lots of contraindications
CTP	High temporal resolution	Radioactivity
	Coronary artery evaluation	Beam hardening artifacts
	Coronary artery evaluation	

PET, Positron emission tomography; SPECT, Single photon-emission CT; MPI, Myocardial perfusion imaging; MR, Magnetic resonance; CTP, CT perfusion.

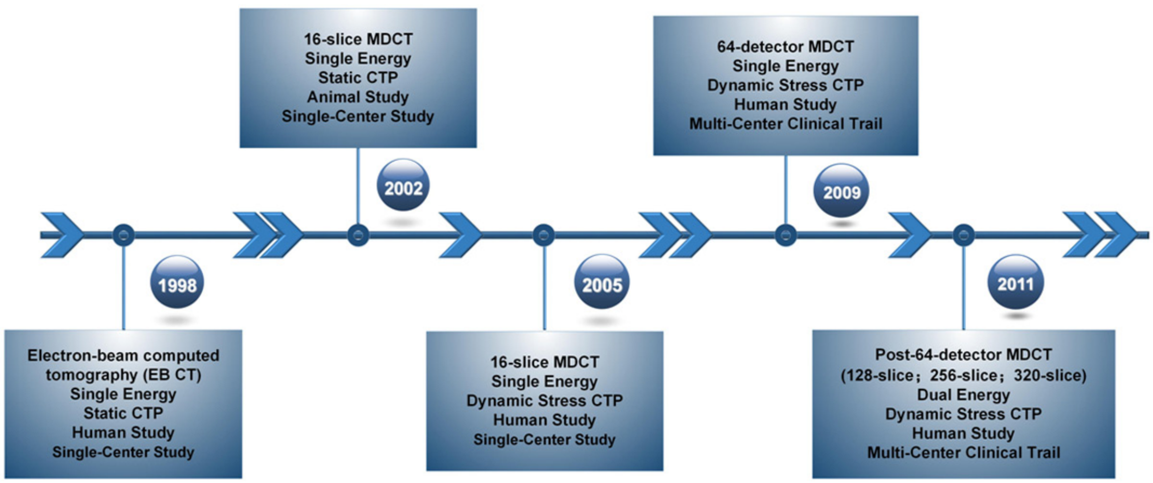

Figure 1. Progress of CTP studies. Over the past few years, CT technology has rapidly developed; scanning modes have evolved from a single spectrum CT to dual-source and dual-energy CTs, and the widths of the detectors have evolved from 4-detector row systems to 64-detector and (more recently) 320-detector systems. The corresponding temporal and spatial resolutions have been greatly improved, and the radiation dose has been significantly reduced.

caused by CAD. Nevertheless, limitations, such as low spatial resolution and complicated operations, still exist. The advantages and limitations of each MPI technique are summarized in **Table 1**.

CTP technology development

Over the past few years, CT technology has rapidly developed. The progress in CTP studies is illustrated in **Figure 1**.

The evolution of the energy spectrum and scanning mode

Recently, CT scanning mode has developed from a single spectrum CT to an era of dual-energy CTs.

Single-spectrum CT: A single-spectrum CT refers to imaging with single energy rays that are emitted from one tube. The gantry rotation and table movement are processed simultaneously to implement helical scanning, which was performed with an earlier-generation 16- or 64-slice multi-detector computed tomography (MDCT). Due to the limited temporal resolution, only first-pass CT perfusion imaging can be performed, i.e., static myocardial CT perfusion scans that prevent the accurate detection of focal ischemia.

Dual-energy CT: In recent years, dual-energy CT myocardial perfusion imaging technology has developed remarkably and can be classified into 3 categories:

Table 2. Comparison of the three categories of dual-energy CT

	Dual-Source system	Single-Source System		Dual-Layer Detector system
X-ray tube	Two	One		One
Detector	Two	One		Two
Tube potential switch	—	During each scan (0.2 ms)	Between each scan (<1 s)	—
Voltage	140 kV (tube A) 80 kV (tube B)	140 kV and 80 kV	135 kV and 80 kV	80/120/140 kV
Temporal resolution	66 ms	165 ms	177 ms	127 ms
Spatial resolution	0.40 mm^3	0.23 mm^3	0.50 mm^3	0.625 mm^3
Scanning time	0.25 s	0.35 s		0.27 s
Heart scanning time	0.25 s	7 s	1-2 s	2 s
Scanning mode	High-spiral acquisition Or shuttle mode	Retrospective ECG-gated spiral acquisition		
Advantage	High temporal resolution	Exact BH correction	Better material decomposition	The two views exactly registered
Disadvantage	Degraded CNR Data truncation artifacts	Imaging artifacts	Motion artifacts	Suboptimal material decomposition BH artifacts
Example of representing vendor	Siemens	GE	Toshiba	Philips

ECG, Electrocardiograph; BH, Beam hardening; CNR, Contrast to noise ratio.

The first type is dual-source CT, which involves two sets of X-ray tubes and detector systems, e.g., the Siemens' Somatom Definition Flash (Siemens Healthcare, Erlangen, Germany), which is mounted on the same rotation gantry with an angular offset of 90 degrees. The x-ray tube-detector pair emits and receives different energy rays at the same time (with 1 tube operating with a low-energy spectrum at 80 or 100 kV and the other operating with a high-energy spectrum at 140 kV) [11, 12]. Then, the gantry rotates 90 degrees to create the reconstructed image. Substantial improvements in temporal resolution and artifact reduction can be achieved by utilizing the table shuttle mode [6, 13, 14] (i.e., the table moves back and forth between the two scanning positions to collect information about the entire heart in the end-systolic phase) or the dual-source-high-pitch scanning mode [15] (i.e., the table is stationary and the gantry moves in the high-pitch spiral scan mode).

Due to the limited space of the gantry, only the high-energy spectrum detector can cover the full available acquisition field of view (AFOV; 50 cm), and the other detector is restricted to a smaller AFOV (26 cm and 33 cm for first- and second-generation scanners, respectively) [16]. Therefore, the resulting data truncation during the scan can yield image artifacts [17].

The second type is single-source dual-energy CT, which involves a single x-ray tube capable of producing x-rays with two different energy spectra. As in the case of the GE Healthcare Discovery CT750 HD scanner (GE Healthcare, Waukesha, WI, USA), the high (140 kV) and low (80 kV) tube voltage switch occurs within each gantry rotation time (0.5 s) and as rapidly as every 0.2 milliseconds (0.0002 second) [18-20]. Each pair of projections is essentially acquired from the same view angle. The advantage is that the corresponding beam hardening (BH) artifact correction will be more accurate than dual-source CT [20]. However, the limitation is that the tube current cannot be modulated at the same speed as the tube potential, which may lead to artifacts. Similarly, a voltage-switching pattern is also included in the Toshiba's Aquilion ONE (Toshiba America Medical Systems, Tustin, CA, USA). The difference is that the high (135 kV) and low (80 kV) tube voltage switches occur between each gantry rotation time. In this approach, the x-ray tube voltage is first set to either to the high or low level to complete the first gantry rotation (scan), and then it is quickly switched to the other kV setting (or vice versa) for the subsequent scan (the switch time is less than one second). The material decomposition in this mode could be better than the others, but the limitation is the motion artifact between the two separate scans [16].

The third type of single-source dual-energy CT is the dual-layer detector system (Philips' prototype), i.e., the x-ray detector consists of two different scintillating materials bound together, and the low stopping power material is placed above the high stopping power material, which allows for higher energy x-ray photons to pass through the top layer without suffering significant attenuation, whereas the lower energy photons are mostly attenuated in the top layer [21]. The bi-layer structure of this "sandwich detector" corresponds to the two types of high and low X-ray energy ranges. Compared with the two former dual energy systems [22], the two projections obtained from the latter bi-layer detector are to some extent difficult to separate from each other, which can could lead to suboptimal material decomposition and BH correction in quantitative MP imaging. A detailed comparison of the three categories of dual-energy CT is summarized in **Table 2**.

Based on the specific attenuation spectral characteristics of the different tissues and iodine contrast agents associated with different X ray energies [23, 24], a dual-energy CT can provide additional information to distinguish the features of the tissue and to construct iodine concentration maps (within the blood vessels and myocardium). A clinical trial of a dual-energy CT revealed that compared with MRI-MPI and ICA on the segment basement, the sensitivity and specificity of CTP in the diagnosis of myocardial perfusion defects are 89%, 78% and 89%, 76%, respectively [25]. This finding was evaluated through reconstructing, post-processing and then integrating the dual-energy data into the iodine concentration map.

The evolution of detectors

Multi-narrow-detector spiral CT: Spiral CT mode means that the table movement and gantry rotation occur at the same time to acquire the image information. The Z-axis coverage ranges of the initial 16- or 64-detector sets are only 2-3.2 cm, which is the main disadvantage. The gantry rotation speed is 400-600 ms/r. The limitations of such detectors include the high levels of artifacts and low temporal resolution, which result in prolonged scanning and breath-holding time. Additionally, the retrospective ECG-triggered scan mode is always selected to maintain the image quality, which further increases the radiation dose. Richard T. George et al. performed a clinical trial of retrospective ECG-triggered stress CTP scans with a 64-detector CT and found that the mean radiation dose was as high as 16.8 mSv, which is even higher than the summation of static and stress SPECT-MPI, the average dose of which is 11-12 mSv [26].

Wide-area multi-detector CT: The appearance of wide-area multi-detector CT enabled a considerable enlargement of the coverage range. The temporal resolution is greatly improved, which cuts down the scan time for the whole heart and makes it possible to complete the heart scan within one cardiac cycle. This advancement accelerated dynamic CTP imaging and the quantitative analysis of MBF. Currently, wide MDCT is mainly included in the Toshiba 320-detector dynamic volume CT (Aquilion ONE) and Philips 256-slice MDCT (Brilliance iCT).

Regarding the former machine, the Z-axis coverage expands from 4 cm to 16 cm and completely covers the entire whole scope of the heart [27]. The gantry rotation speed is 350 ms/r. The temporal resolution of a half rotation is 175 ms, and with the table stationary mode, the breath-holding time is shortened to 1-2 s. The scan typically starts in the middle of diastole. Moreover, the prospective ECG-triggered scan mode is available to significantly reduce the radiation dose.

Regarding the latter machine, due to the increase in the number of detector rows, the Z-axis coverage reaches 78 mm [15, 28]. Under wide-area MDCT scanning, the CTP image information within one cardiac cycle can be collected and evaluated at any time [26]. Therefore, the artifact correction can be improved to further reduce noise and achieve much better image quality. Dynamic CTP scanning with the Philips 256-slice MDCT can reduce the radiation dose to 9.5 mSv, which is comparable to that of dual-source CT [15]; it can even reduce the dose to as low as 5.4 mSv [26]. The CORE320 multi-center clinical trial [4, 28] aimed to evaluate the practicability and diagnostic value of CTA and CTP with the 320-row dynamic volume CT and has been completed, and the clinical application value has been already been confirmed.

The evolution of image analysis technology

Qualitative analysis: The X-ray attenuation degree of the iodine contrast medium in CTP is

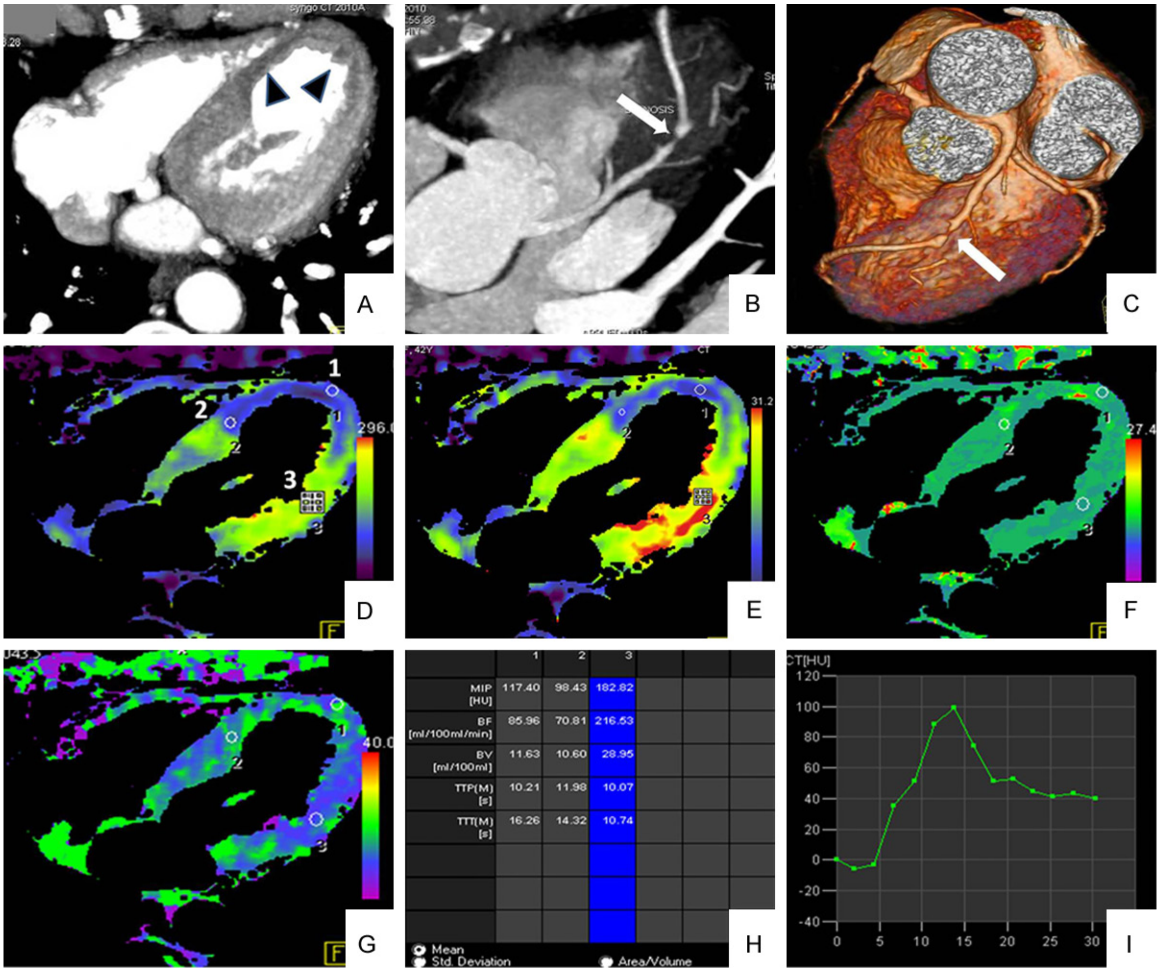

Figure 2. A 43-year-old woman with hypertension and atypical chest pain. (A) Visual assessment of a stress CT perfusion axial image reveals a low-density area in the interventricular septum and the left ventricular anterior wall (black triangle arrows). (B, C) A maximum intensity projection (MIP, B) and volume rendering (VR, C) of a CT angiograph reveals shows significant stenosis (white arrow) in the mid-left anterior descending coronary artery. (D-H) All of the quantitative parameters, including the MBF (D), MBV (E), TTP (F), TTT (G) and local hemodynamic absolute numbers (H) demonstrate the anterior perfusion defect (1 and 2) compared with a normal myocardium (3). (I) ROI-TAC of a normal myocardium (3).

proportional to the iodine concentration density, which means that low density areas represent hypoperfused areas. The technique of qualitative analysis detects the presence of ischemia or infarction by visually comparing the region of interest (ROI) with the normal myocardium at a distance, which is the most simple and common analysis method. However, to accurately detect the hypoperfusion area, the acquisition time for CTA images should occur during the peak myocardial contrast enhancement, which cannot always be guaranteed. Additionally, when universal myocardial ischemia exists, it may be difficult to achieve an accurate diagnosis with the qualitative analysis method.

Quantitative analysis: Quantitative analysis includes semi-quantitative analysis and quantitative analysis, and the analysis results of the latter technique are much more accurate than those of the former [29]. Compared with qualitative analysis, assessments with the quantitative analysis technique are much more precise and effective, and the greatest advantage is the ability to draw time-attenuation curves for the region of interest (ROI-TAC) [30] to calculate and analyze the corresponding hemodynamic parameters, such as the myocardial blood flow (MBF), myocardial blood volume (MBV), up-slope, peak enhancement, time to peak (TTP), tissue transit time (TTT), area under the curve (AUC), etc., which enables comprehensive and

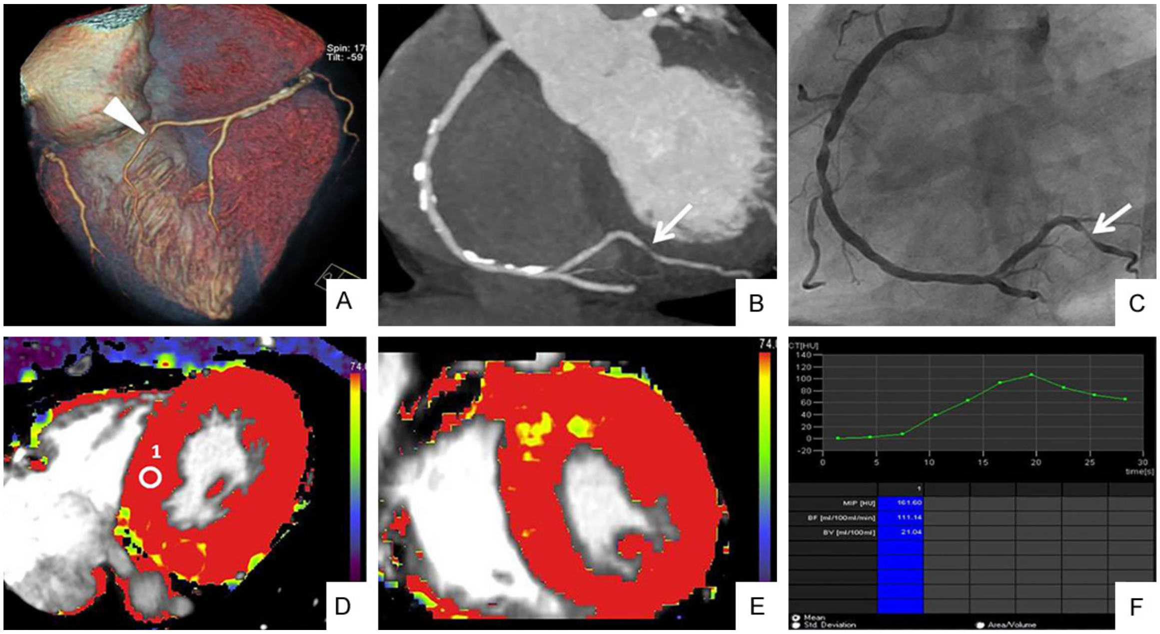

Figure 3. A 65-year-old man with chest tightness. (A, B) Volume rendering (VR, A) and maximum intensity projection (MIP, B) of a CT angiograph revealing significant stenosis (white triangle and white arrow) in the distal segment of right coronary artery (RCA) at the bottom of the left ventricle. (C) Significant stenosis in the distal segment of the RCA (white arrow) confirmed by coronary angiography (CAG, C). (D-F) MBF (D, E) of a stress CTP showing no perfusion decrease in the interventricular septum myocardium or the inferior myocardium of the left ventricle. The local hemodynamic absolute number (H) and TAC are normal. Within 2-5 years of follow-up, this patient had no major adverse cardiovascular events (MACE), including cardiac death, non-fatal myocardial infarction (MI), unstable angina (UA), or revascularization.

quantitative evaluation of the myocardial perfusion (**Figures 2** and **3**).

Compared with normal myocardium, ischemic myocardium exhibits decreased wash-in and a delayed TTP, and infarcted myocardium exhibits both a slow wash-in and a slow washout of the contrast medium, which results in a delayed TTP and a lower peak attenuation [6]. It has also been reported that in regard to detecting diffuse myocardial ischemia and ischemic severity classification, the quantitative analysis of hemodynamic parameters is highly superior [31].

Clinical relevance

With the evolution of CT technology, CTP clinical trials have become prevalent around the world. The diagnostic accuracy of CTP for myocardial ischemia and its strong relevance to SPECT-MPI and CAG have already been confirmed by several single-center clinical trials [32, 33] and the CORE320 multicenter, multinational diagnostic study [4, 5]. Furthermore, compared with single CTA, CTP combined with CTA can effectively improve the diagnostic accuracy and reduce the radiation dose [4]. Nevertheless, wider multi-center clinical trials are still needed to verify both the clinical application value of CTP imaging and its prognostic significance, which can be investigated and validated with the follow-up studies of major adverse cardiovascular events (MACE) following CTP imaging (**Figure 3**).

The limitations and direction of developments in CTP technology

Artifacts

Artifacts often affect the sensitivity and accuracy of the diagnosis. The common artifacts include motion artifacts, beam-hardening artifacts, and reconstruction artifacts. It is helpful to minimize artifacts to enhance the image quality and diagnostic accuracy by means of adopting prospective scans, improving the speed of the gantry rotation (which increases the temporal resolution), employing 320-row detectors, controlling the heart rate, ameliorating algorithms, and using the beam-hardening correction algorithms [34]. It has also been reported that rapidly switching dual-energy CT can reduce beam-hardening effects [6].

Radiation dose

A high radiation dose has been considered to be the main obstacle to the routine application of CTP [35]. In recent years, with the substantial improvement in CT technology, the temporal resolution has significantly increased. Consequently and in combination with several radiation dose control strategies, such as low tube voltage imaging and automatic tube current adjustments, the radiation dose of continuous scanning has been significantly reduced. More recent data have demonstrated that the mean radiation dose of static CTP imaging is 3.3-4.6 mSv [36], and the mean effective radiation dose of dynamic CTP imaging has been reduced to 9.2-10.0 mSv [14, 37]. It has been reported that the use of high-pitch flash spiral scans with the SAFIRE technique in DSCT-equipped IC detectors can greatly reduce the radiation dose of CTP while guaranteeing the image quality [37].

Contrast agents

The contrast volume of the CTP is much greater than that of coronary CTA. For patients with renal function deficiencies, more caution is required. In addition to efforts to reduce the dose of the contrast agent, researching and developing new types of safe and feasible contrast materials are equally important.

Directions of development

With the rapid development of CT technology and post-processing, CTP has begun to demonstrate its great advantages and application prospects in the diagnosis of CAD. Furthermore, due to the recent introduction of third-generation dual-source CT systems (Force CT) [38, 39] and their availability for clinical use, technical refinements (including wider detector coverages, increased rotation speeds, more advanced iterative reconstructions, etc.) will provide great opportunities to for CTP examinations to be become universally and widely implemented.

Conclusion

CT technology has been constantly developed in recent decades, and the safety and feasibility of myocardial CT perfusion imaging have already been demonstrated. However, this technique is still in the stage of clinical trials and preliminary applications, and studies of CTP and its significance for clinical prognoses are relatively scarce. Such studies are widely needed. Additionally, further efforts to reduce the radiation dose associated with CTP are another avenue of research and development. Based on all of the considerable advantages of CTP and the advancement of CT technologies, the forthcoming ubiquitous use of CTP is definitely to be expected.

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Disclosure of conflict of interest

None.

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