Dynamic CT Perfusion Imaging: State of the Art

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Recent advances in computed tomography (CT) technology have enabled stress dynamic CT perfusion (CTP) imaging of the entire myocardium to be performed with high temporal resolution and reasonable radiation dose. The most important advantage of dynamic CTP is the feasibility of complete quantification of myocardial perfusion in mL/min/g. Although high diagnostic values have been reported for the detection of myocardial ischemia, standardization of acquisition method, mathematical modeling and interpretation, as well as further evaluation of its accuracy, clinical role, and cost effectiveness are required before its routine clinical implementation. The current review focuses on the state-of-the-art of dynamic CTP and outlines its current status and future directions as a new technology for the physiologic assessment of coronary artery disease.

Key words Multidetector computed tomography · Myocardial perfusion imaging · Coronary artery disease.

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INTRODUCTION

Over the last two decades, computed tomography (CT) has made significant advancement. Coronary CT angiography (CCTA), which first appeared in 2001 in the literature, is now widely performed for patients with suspected and known coronary artery disease (CAD). CCTA has high sensitivity (94–99%) and specificity (64–83%) and a negative predictive value (NPV) of 97–99% for detecting obstructive CAD [1]. A recent prospective multicenter randomized controlled trial that assessed the role of CCTA in >4000 patients with suspected angina due to coronary heart disease demonstrated that, when included in the initial assessment of chest symptoms, CCTA can contribute to more accurate diagnosis of CAD, more efficient downstream testing, and more appropriate treatments [2]. More importantly, fatal and nonfatal myocardial infarction was halved in patients allocated to CCTA compared with those assigned to standard care [3]. In response to the results of the randomized trial, the National Institute for Health and Care Excellence in the United Kingdom updated its clinical guideline for chest pain of recent onset so that CCTA is recommended as the first-line test [4].

Although CCTA is a robust technique for assessing morpho-

logical stenosis and plaque burden of coronary artery, it is limited in determining the hemodynamic significance of coronary stenoses. Solely with morphological assessment of stenosis, CCTA can provide only poor correlation with evidence of myocardial ischemia and a positive predictive value (PPV) of 29–58% [5]. Considering the growing evidence of the benefit of the physiology-guided coronary revascularization strategy [6–8], routine integration of anatomical information by CCTA and location, extent, and severity of ischemia should be valuable. Such information can be obtained through non-invasive functional imaging such as single photon emission computed tomography (SPECT), positron emission tomography (PET), or stress perfusion magnetic resonance imaging (MRI). However, CT is evolving to a standalone modality for comprehensive assessment of anatomical stenosis and its hemodynamic significance in the same examination due to the remarkable advance of CT systems and post-processing. Actually, CT-derived fractional flow reserve (FFR) and stress CT perfusion (CTP) imaging are currently under intensive investigation. Given different underlying physical principles and the types of pathophysiological information they provide, these techniques have their own advantages and disadvantages [9] and may have complementary clinical roles. But it should be noted that CTP is not a computer simulation, but assesses what is happening *in vivo* with unprecedented spatial resolution, which may contribute to advance

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our understanding of myocardial perfusion at the microcirculatory level.

There are currently two approaches in CTP—static and dynamic. Static CTP imaging refers to the assessment of myocardial enhancement acquired at a single time point of the first-pass of contrast material bolus. Since the first human report of CTP under adenosine stress by Kurata et al. [10], static CTP has been evaluated by many single and multicenter studies because of its technical ease of implementation—static CTP can be performed on any CT platform that is capable of CCTA. However, success of perfusion assessment by static CTP is highly dependent on contrast material bolus timing [11–14] and motion [15,16]. In contrast, with a dynamic approach, myocardial perfusion is assessed based on myocardial enhancement at multiple time points of first-pass of the contrast material, which is robust in terms of bolus timing and allows for fully quantitative analysis of myocardial perfusion. Although clinical implementation of dynamic CT perfusion has been a challenge because of its limited z-axis coverage (~4 cm) of 64-detector row CT scanners and relatively high radiation dose inherent to repetitive image acquisition, recent advances in CT technology allow dynamic CTP of the entire myocardium to be performed at reasonably reduced radiation exposure. The purpose of this review is to describe the state-of-the art of dynamic CTP including advantages and disadvantages of different CT platforms.

PREREQUISITES FOR DYNAMIC CTP

In order to obtain high quality dynamic CTP images, a high temporal resolution and wide detector coverage along the z-axis are essential. In Table 1, characteristics of commercially available CT scanners capable of dynamic CTP with wide z-axis coverage are summarized.

High temporal resolution

The most common and basic approach to optimize temporal resolution for CCTA is half-scan reconstruction (180-degree reconstruction). However, reconstruction using a wider array of projections is advantageous for CT number accuracy since adding projections beyond 180° improves the signal-to-noise

ratio [17], reduces streak and partial scan artifacts [18–20], and enables reconstruction of wider z-axis coverage [21]. For dual-source CT scanners, 180° (=90° rotation) and 360° (=270° rotation) reconstruction are blended after filtering, thus preserving high temporal resolution of half scan and CT number stability of full scan [19,22]. However, 360° rotation data are more commonly used for dynamic CTP with wide-detector CT scanners [21,23,24]. Considering that successful vasodilator-stress results in heart rate increase >10 beats per minute, current temporal resolution of multidetector CT (≥ 250 ms with full-scan reconstruction) requires further improvement [25]. Motion artifacts due to increased heart rate during adenosine stress have been observed in a significant percentage of patients in static CTP [16]. At present, systolic acquisition appears to be a reasonable strategy because systole has a stable length of approximately 200 ms, is less sensitive to RR variability and arrhythmia, and is less prone to artifacts due to its thicker myocardium [26]. In addition, the thicker myocardium allows easier contour delineation and evaluation of transmural contrast enhancement.

Wide-detector coverage

In order to obtain whole heart dynamic CTP with high sampling rate of each heartbeat, wide-detector CT scanners with z-axis coverage of 16 cm is essential. Although (sub-)total coverage of left-ventricular myocardium is feasible by narrower detector scanners with shuttle mode, the sampling rate for a given part of myocardium is not high: every second heart beat for a heart rate of 63 beats per minute or less and every forth heart beat for a heart rate greater than 63 beats per minute [26,27]. Moreover, combination of temporally different cranial and caudal parts can potentially associate image artifacts along the border of the 2 parts. In these regards, area-detector CTs have distinct advantages over dual-source CTs. An additional advantage of wider-detector CT is the ability to acquire CCTA during the dynamic scan [23]. On the other hand, the capability for wide z-axis dynamic imaging of every heart beat can easily lead to excessive radiation. Every dose reduction strategy such as low-tube-voltage setting, tube current modulation, and reduction of dynamic phases should be considered to avoid unneeded radiation exposure.

Table 1. Characteristics of computer tomography scanners capable of dynamic CTP with wide z-axis coverage

Manufacturer	Model	Number of detector-rows	Z-axis coverage of dynamic CTP (mm)	Rotation speed (ms)	Half scan temporal resolution (ms)
Canon	GENESIS/ViSION	320	160	275	138
GE	Revolution	256	160	280	140
Philips	iCT	128	78	270	135
Siemens	Force	96	105 (shuttle mode)	250	66 (dual-source)
Siemens	Drive/ Flash	64	73 (shuttle mode)	280	75 (dual-source)

CTP: computed tomography perfusion

Beam hardening correction and noise reduction

The beam-hardening effect is caused by preferential absorption of low-energy photons as a polychromatic X-ray beam passes through an object. The resulting filtered beam with higher mean energy can result in so-called beam hardening artifacts typically recognized as low-attenuation between high attenuation structures. Conventional beam-hardening correction algorithms used in body CT imaging have been specifically optimized to correct beam-hardening artifact from bone, which is the most substantial high-attenuation source of beam hardening. For accurate assessment of myocardial perfusion, beam hardening effects from temporally variable high attenuation in heart chambers and great vessels caused by iodine contrast material also need to be managed [28]. In dynamic CTP, the time-dependent iodine distribution and its resulting beam hardening effect can be calculated by analyzing the temporal voxel changes, thus distinguishing from beam hardening effects from other high-attenuation materials such as bone [29,30]. This type of spatio-temporal analysis also greatly contributes to noise reduction (and eventually dose reduction) of dynamic CTP [25,29,30] and may be combined with iterative reconstruction algorithms [31,32].

QUANTITATIVE MYOCARDIAL PERFUSION ESTIMATION

The most important advantage of dynamic CTP over static CTP is the feasibility of full quantification of myocardial perfusion in mL/min/g. Although there are a number of approaches for full quantification [33,34], the maximum slope model has been used in most previous patient studies with only a few exceptions (model-based deconvolution [24] and single-tissue compartment model [23]). In the maximum slope method, myocardial blood flow (MBF) is estimated as the ratio of the maximum instantaneous slope of the myocardial iodine enhancement curve to the maximum value of the input function, multiplied by the reciprocal of the tissue density based on the assumption that the rate of arrival of contrast agent is proportional to the tissue perfusion level [34]. However, mathematically, MBF determined by the equation is equal to the blood-to-myocardium transfer constant, K_{tr} in the Patlak model, which requires flow-dependent extraction fraction of contrast medium to be converted to MBF [35,36]. In addition, limited sampling rate may lead to substantial underestimation of MBF [35]. Expected systemic underestimation of MBF by the maximum slope method has been seen experimentally in comparison with microsphere-derived MBF [37,38]. Nonetheless, it has been demonstrated in porcine animal models that CT-derived MBF based on the maximum slope method shows good correlation with coronary artery blood flow and fractional flow reserve (FFR) [39,40] and permits more

accurate demonstration of the hemodynamic effect of moderate (50%) coronary stenosis compared to measurement of myocardial enhancement at single-phase high-pitch acquisition [41]. In our experience, quantitative analysis is more sensitive for hypoperfusion than visual assessment of dynamic CT image datasets (Fig. 1) and improves inter-observer agreement for detecting significant CAD. Further investigation is warranted for reliability of MBF quantification by CT regarding its test-retest reproducibility and correlation with ^{15}O -water PET, which is the established clinical standard for MBF quantification. Furthermore, lack of standardized acquisition and modeling protocols for MBF quantification complicates the generalization of study results obtained using a different CT protocol and/or mathematical modeling.

DIAGNOSTIC PERFORMANCE OF DYNAMIC CTP

Diagnostic performance of dynamic CTP has been validated against different reference standards including MRI [42-45], SPECT [43,46,47], and coronary angiography with FFR measurement [21,27,48-53]. Available data are scarce on the diagnostic performance of dynamic CTP for detecting perfusion defects determined by MRI or SPECT. However, reported segment-based sensitivity and specificity of dynamic CTP are 78-81% and 75-94%, respectively, when MRI is used as the reference [44,45]. These values are 83-85% and 78-92%, respectively, in comparison with SPECT [46,47]. So far, there are 8 single center studies evaluating dynamic CTP with FFR as the reference standard (Table 2). The sensitivity, specificity, PPV, and NPV range from 73-98%, 68-100%, 49-100%, and 74-98%, respectively, with pooled sensitivity of 84% and pooled specificity of 80%. It has been demonstrated that specificity and PPV of CCTA can be improved with quantitative dynamic CTP [45,50].

In all studies except one by Huber et al. [21], dual-source CT and its commercially available perfusion quantification software were used for the evaluation of diagnostic accuracy. As summarized in Table 2, in spite of the use of the same CT technology and mathematical algorithm and relatively small variation in the mean MBF values in ischemic myocardium (70-79 mL/100 mL/min), the best cut-off MBF value for distinguishing ischemic and remote myocardium varies from 75 to 103 mL/100 mL/min. This wide range of cut-off values may be related to differences in study design, patient risk profile, prevalence of CAD, and FFR threshold. In addition, hyperemic MBF in remote myocardium can be influenced by other factors such as age, gender, race, BMI, insulin resistance, arteriolar response to vasodilators, and presence of collateral vessels [54-57]. Debatably, relative MBF normalized by remote MBF may provide more accurate identification of hemodynamically significant CAD than abso-

Fig. 1. A 58-year-old male with stenting to the LAD artery. Coronary CT angiography demonstrated moderate stenosis in the proximal LAD (green arrow) and an occluded diagonal branch (yellow arrow) (A). Reduced perfusion was hardly recognized on CT perfusion images of 8 continuous dynamic phases (B) but was evident in the anterior wall (arrows) subtended by the occluded diagonal branch on the myocardial blood flow map (C). Delayed enhancement CT revealed presence of infarcted myocardium in the area (D). LAD: left anterior descending, CT: computed tomography.

Table 2. Vessel-based diagnostic accuracy of dynamic CT perfusion compared with invasive coronary angiography with fractional flow reserve for the diagnosis of hemodynamically significant coronary artery disease

Author	N	CT scanner	SE (%)	SP (%)	PPV (%)	NPV (%)	MBF stress remote	MBF stress ischemic	Best MBF cut-off	Radiation dose (mSv)
Bamberg et al. [27]	33	Flash	93	87	75	97	105±34	73±26	75	10.0 [†]
Greif et al. [48]	65	Flash	95	74	49	98	123±34	79±26	75	9.7 [†]
Huber et al. [21]	32	iCT	76	100	100	91	310±130	150±160	164	9.5 [†]
Rossi et al. [50]	80	Flash	88	90	77	95	100 (83–119)	70 (62–76)	78	9.4 [‡]
Kono et al. [49]	42	Flash	98	70	76	97	116±27	76±23	103*	9.4 [‡]
Goto et al. [53]	51	Flash	84	84	82	86	99±36	74±27	89*	5.3 [‡]
Coenen et al. [52]	43	Flash	75	78	78	75	92±23	71±24	76	9.0 [‡]
		Force								
Coenen et al. [51]	74	Flash	73	68	67	74	108	79	91	9.3 [‡]
		Force								
Pooled	420		84	80	72	88	106.5 (median)	75 (median)	83.5 (median)	8.4 [‡]

MBF was presented in mL/100 mL/min. *best diagnostic performance was achieved based on relative MBF cut-off (Kono et al. [49] MBF ratio of 0.85; Goto et al. [53] transmural perfusion ratio of 0.899), [†]conversion factor=0.017, [‡]conversion factor=0.014. N: number of patients, MBF: myocardial blood flow, NPV: negative predictive value, PPV: positive predictive value, SE: sensitivity, SP: specificity

lute MBF [49,53]. We should also recognize that FFR is a measure of lesion specific hemodynamic significance of stenosis, not a measure of myocardial perfusion, which is governed by not only epicardial coronary stenosis, but also microvascular environment and collateral circulation. In order to enable accurate interpretation of quantitative MBF values, a large database on normal values including physiological regional heterogeneity and establishment of the prognostic implication of MBF value

are arguably necessary. Only limited data are available on normal MBF values at this point [58,59] (Table 3).

RADIATION OF DYNAMIC CTP

Radiation exposure associated with dynamic CTP remains a concern. The average effective radiation dose ranges between 5.3 mSv to 10.0 mSv in the previous reports listed in Table 3.

Table 3. MBF values in normal volunteers and low risk subjects

Author	N	CT scanner	Subjects	Age (yr)	MBF stress	MBF rest	Perfusion reserve
Kim et al. [58]	19	Flash	Healthy volunteers	33–60	173±33	83±21	2.20±0.53
Ho et al. [59]	35	Flash	Low-risk individuals	25–64	135±29	74±16	1.86±0.38

MBF was presented in mL/100 mL/min. N: number of patients, MBF: myocardial blood flow, CT: computed tomography

However, use of a low tube voltage protocol (80 kV/379 mA) instead of a conventional protocol (100 kV/300 mAs) enables 40% dose reduction without affecting image quality or MBF quantification in patients with normal body mass index [60]. In addition, use of an automatic exposure control system could substantially reduce radiation dose [61]. Dynamic CTP with 3.5 mSv has been reported with a combined use of 70 kVp and an automatic exposure control system [62].

IMPLEMENTATION OF STRESS DYNAMIC CTP IN COMPREHENSIVE CARDIAC CT

In clinical practice, stress dynamic CTP is often implemented as a part of a comprehensive cardiac CT protocol together with other modules such as CCTA, rest dynamic CTP, and CT delayed enhancement.

CCTA

CCTA is generally considered an essential module in a comprehensive cardiac CT. Most reports on CTP perform CCTA and CTP within a single imaging session. However, considering the recent wide-spread use of CCTA in clinical practice, once established as an accurate myocardial perfusion imaging, CTP may be performed independently as a second-line test when CCTA shows CAD of uncertain functional significance or is non-diagnostic. With a wide-area detector with 16 cm z-axis coverage, CCTA may be acquired during rest dynamic CTP [23].

Rest dynamic CTP

Rest dynamic CTP has been performed in few limited research environments [23,58,59,63]. This is simply because CCTA has higher priority than quantitative perfusion information at resting state. Although rest dynamic CTP allows calculation of coronary flow reserve (CFR), PET studies have shown that hyperemic MBF alone may perform equally as well as CFR for detecting coronary stenosis [64,65]. Having said that, a new study has suggested the prognostic value of integrated assessment of hyperemic MBF and CFR [66]. In a clinical scenario where dynamic CTP is used as a second-line test, performing both stress and rest dynamic CTP may be an attractive strategy.

Delayed enhancement

CT delayed enhancement (CTDE) shares the same pathophysiological principle with delayed enhancement MRI, allowing

Fig. 2. Image acquisition timeline of a comprehensive cardiac CT study. Calcium scoring, stress dynamic CTP, rest CCTA, and CTDE can be performed in 30 minutes. CT: computed tomography, CTP: CT perfusion, CCTA: coronary CT angiography, CTDE: CT delayed enhancement.

infarct detection and viability assessment. Side-by-side comparison of stress CTP and CTDE is useful for accurate differentiation between ischemic and infarcted myocardium. Unfortunately, CTDE is not widely used due to low contrast-to-noise ratio; however, its quality has been significantly improved with the recent advancement in image acquisition, reconstruction, and post-processing [67–69]. Assessment of myocardial delayed enhancement appears to be especially important in the delineation of ischemic but viable myocardium in patients with history of myocardial infarction and/or prior stent implantation [53]. Moreover, CTDE may be used to estimate extracellular volume fraction of the left ventricular myocardium [70,71].

Stress CTP first vs. CCTA first

Stress CTP first, followed by CCTA is preferred for the detection of myocardial ischemia because the stress scan will produce “clean,” uncontaminated data. After the stress scan, beta blockers and sublingual nitroglycerin can be administered to optimize CCTA. A timeline of a comprehensive cardiac CT protocol is presented in Fig. 2. CCTA first, followed by stress CTP may appear clinically reasonable since stress CTP can be avoided when obstructive CAD is excluded by CCTA. However, this is not true because of the difficulty of assessing CCTA and deciding whether or not to proceed to stress CTP. Moreover, the time slot required for CCTA becomes unpredictable, which causes substantial inconvenience in scheduling of CT scans. From a technical perspective, cross-contamination of contrast in the stress perfusion scan and beta blockers used to optimize CCTA may mask ischemia. In addition, refrainment from caffeine 24 hours before CT may not be achieved thoroughly in this approach due to the optional nature of the stress scan.

REAL-WORLD INTERPRETATION OF DYNAMIC CTP

Stress myocardial perfusion can be considered normal when uniformly high (i.e., >110 mL/100 mL/min for dual-source CT and maximum slope method) MBF is demonstrated (Fig. 3). Uniformly low MBF (<75 mL/100 mL/min) is rarely seen, but is most likely due to no or insufficient hyperemic response to vasodilators, which may hamper ischemia detection (Fig. 4). Once sufficient hyperemia is confirmed by high MBF in remote myocardium, hemodynamic significance of coronary artery stenosis may be assessed based on absolute MBF value in the vessel territory (Fig. 5). However, as discussed earlier, a universally applicable MBF threshold for myocardial ischemia

may not exist since normal MBF varies from patient to patient. Therefore, it is important to consider relative MBF values in the final judgement of ischemia (Fig. 6). Moreover, reduction of perfusion may be observed in the absence of obstructive CAD as a result of microvascular dysfunction (Fig. 7). Assessment of hemodynamic significance of epicardial coronary stenosis is a challenge in the presence of concomitant microvascular dysfunction.

CONCLUSIONS

Dynamic CTP is a novel myocardial perfusion imaging technique that may open the era of routine absolute quantification of MBF. However, it is a still-nascent technology, and standard-

Fig. 3. Basal, mid, and apical short axis (A, B, and C) and horizontal long axis (D) stress dynamic computed tomography-derived MBF maps of the left ventricle with a color-coded overlay showing uniformly normal absolute MBF values (200–230 mL/100 mL/min) in a 54-year-old female with suspected coronary artery disease. Curved multiplanar reformatted images of the left anterior descending (E), right coronary artery (F), and left circumflex artery (G) and three-dimensional volume rendered images (H), all show normal coronary arteries. MBF: myocardial blood flow.

Fig. 4. Basal, mid, and apical short axis (A, B, and C) and horizontal long axis (D) stress dynamic computed tomography-derived MBF maps of the left ventricle with a color-coded overlay in a 70-year-old male with suspected coronary artery disease showing uniformly reduced absolute MBF values (70–80 mL/100mL/min). Curved multiplanar reformatted images of the left anterior descending (E), right coronary artery (F), and left circumflex artery (G) show no significant coronary artery stenosis. MBF: myocardial blood flow.

Fig. 5. In a 72-year-old female with dyslipidemia and diabetes who presented with electrocardiogram abnormality, coronary computed tomography angiography demonstrated severe stenosis (yellow arrow) in the left descending artery (A) and no significant stenosis in the left circumflex artery (B) or right coronary artery (C). Dynamic computer tomography perfusion images in the short axis (D) showed reduced myocardial blood flow in the left descending artery territory.

Fig. 6. In a 52-year-old female with hypertension, dyslipidemia, and diabetes who presented with atypical chest pain, coronary CT angiography (A) and invasive coronary angiography (B) demonstrated moderate stenosis in the proximal left descending artery (yellow arrow) and severe stenosis in the diagonal branch (green arrow). Dynamic CT perfusion images in the short axis (C) showed MBF values of 100–110 mL/100mL/min in the diagonal branch territory, which were substantially lower compared with remote segments (170–180 mL/100 mL/min). Although absolute MBF in the diagonal branch territory was well above thresholds of myocardial ischemia (75–103 mL/100 mL/min) in the literature, concordance of stenosis and relative reduction of MBF suggested its hemodynamic significance. CT: computed tomography, MBF: myocardial blood flow.

ization of acquisition method, mathematical modeling, and interpretation remain to be achieved. Nonetheless, high diagnostic values of dynamic CTP are seen for the detection of myocardial ischemia determined by FFR. In addition, cardiac CT has the advantage of providing integrated information of morphology

and function in a single examination. Large-scale clinical trials are warranted to further evaluate its accuracy, clinical role, and cost effectiveness.

Fig. 7. This figure shows images of an 85-year-old male with hypertension. On coronary CT angiography, only mild calcified plaque was present in the left descending artery (B), and no plaque or stenosis was detected in the right coronary artery (A) or the left circumflex artery (C). Left ventricular hypertrophy was not present (not shown). Dynamic CT perfusion images demonstrated sub-endocardial reduced perfusion diffusely distributed from base to apex (D). This stress perfusion finding was attributed to microvascular dysfunction in the absence of obstructive stenosis in the epicardial coronary arteries. CT: computed tomography.

Conflicts of Interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Marwick TH, Cho I, Ó Hartaigh B, Min JK. Finding the gatekeeper to the cardiac catheterization laboratory: coronary CT angiography or stress testing? *J Am Coll Cardiol* 2015;65:2747-2756.
2. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet* 2015;385:2383-2391.
3. Williams MC, Hunter A, Shah ASV, Assi V, Lewis S, Smith J, et al. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol* 2016;67:1759-1768.
4. Adamson PD, Hunter A, Williams MC, Shah AS, McAllister DA, Pawade TA, et al. Diagnostic and prognostic benefits of computed tomography coronary angiography using the 2016 National Institute for Health and Care Excellence guidance within a randomised trial. *Heart* 2018;104:207-214.
5. Blankstein R, Di Carli MF. Integration of coronary anatomy and myocardial perfusion imaging. *Nat Rev Cardiol* 2010;7:226-236.
6. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al.; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503-1516.
7. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al.; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991-1001.
8. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, et al. Angiographic versus functional severity of coronary artery ste-

- noses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010;55:2816-2821.
9. Schuijff JD, Ko BS, Di Carli MF, Hislop-Jambrich J, Ihdahid AR, Seneviratne SK, et al. Fractional flow reserve and myocardial perfusion by computed tomography: a guide to clinical application. *Eur Heart J Cardiovasc Imaging* 2018;19:127-135.
 10. Kurata A, Mochizuki T, Koyama Y, Haraikawa T, Suzuki J, Shigematsu Y, et al. Myocardial perfusion imaging using adenosine triphosphate stress multi-slice spiral computed tomography: alternative to stress myocardial perfusion scintigraphy. *Circ J* 2005;69:550-557.
 11. Bischoff B, Bamberg F, Marcus R, Schwarz F, Becker HC, Becker A, et al. Optimal timing for first-pass stress CT myocardial perfusion imaging. *Int J Cardiovasc Imaging* 2013;29:435-442.
 12. Otton J, Morton G, Schuster A, Bigalke B, Marano R, Olivotti L, et al. A direct comparison of the sensitivity of CT and MR cardiac perfusion using a myocardial perfusion phantom. *J Cardiovasc Comput Tomogr* 2013;7:117-124.
 13. Pelgrim GJ, Nieuwenhuis ER, Duguay TM, van der Geest RJ, Varga-Szemes A, Slump CH, et al. Optimal timing of image acquisition for arterial first pass CT myocardial perfusion imaging. *Eur J Radiol* 2017;86:227-233.
 14. Tanabe Y, Kido T, Kurata A, Uetani T, Fukuyama N, Yokoi T, et al. Optimal scan time for single-phase myocardial computed tomography perfusion to detect myocardial ischemia. Derivation cohort from dynamic myocardial computed tomography perfusion. *Circ J* 2016;80:2506-2512.
 15. Yang DH, Kim YH, Roh JH, Kang JW, Han D, Jung J, et al. Stress myocardial perfusion CT in patients suspected of having coronary artery disease: visual and quantitative analysis-validation by using fractional flow reserve. *Radiology* 2015;276:715-723.
 16. van Rosendaal AR, de Graaf MA, Dimitriu-Leen AC, van Zwet EW, van den Hoogen IJ, Kharbada RK, et al. The influence of clinical and acquisition parameters on the interpretability of adenosine stress myocardial computed tomography perfusion. *Eur Heart J Cardiovasc Imaging* 2017;18:203-211.
 17. Abbata S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the society of Cardiovascular Computed Tomography Guidelines Committee: Endorsed by the North American Society for Cardiovascular Imaging (NASCI). *J Cardiovasc Comput Tomogr* 2016;10:435-449.
 18. Primak AN, Dong Y, Dzyubak OP, Jorgensen SM, McCollough CH, Ritman EL. A technical solution to avoid partial scan artifacts in cardiac MDCT. *Med Phys* 2007;34:4726-4737.
 19. Ramirez-Giraldo JC, Yu L, Kantor B, Ritman EL, McCollough CH. A strategy to decrease partial scan reconstruction artifacts in myocardial perfusion CT: phantom and in vivo evaluation. *Med Phys* 2012;39:214-223.
 20. Stenner P, Schmidt B, Bruder H, Allmendinger T, Haberland U, Flohr T, et al. Partial scan artifact reduction (PSAR) for the assessment of cardiac perfusion in dynamic phase-correlated CT. *Med Phys* 2009;36:5683-5694.
 21. Huber AM, Leber V, Gramer BM, Muenzel D, Leber A, Rieber J, et al. Myocardium: dynamic versus single-shot CT perfusion imaging. *Radiology* 2013;269:378-386.
 22. Bruder H, Raupach R, Klotz E, Stierstorfer K, Flohr T. Spatio-temporal filtration of dynamic CT data using diffusion filters. *Proceedings of SPIE Medical Imaging*; 2009 Feb 7-12; Lake Buena Vista (Orlando Area), Florida, United States. *Proc SPIE* 7258, Medical Imaging 2009: Physics of Medical Imaging.725857.
 23. Kikuchi Y, Oyama-Manabe N, Naya M, Manabe O, Tomiyama Y, Sasaki T, et al. Quantification of myocardial blood flow using dynamic 320-row multi-detector CT as compared with 150-H₂O PET. *Eur Radiol* 2014;24:1547-1556.
 24. Kurata A, Kawaguchi N, Kido T, Inoue K, Suzuki J, Ogimoto A, et al. Qualitative and quantitative assessment of adenosine triphosphate stress whole-heart dynamic myocardial perfusion imaging using 256-slice computed tomography. *PLoS One* 2013;8:e83950.
 25. Muenzel D, Kabus S, Gramer B, Leber V, Vembar M, Schmitt H, et al. Dynamic CT perfusion imaging of the myocardium: a technical note on improvement of image quality. *PLoS One* 2013;8:e75263.
 26. Mahnken AH, Klotz E, Pietsch H, Schmidt B, Allmendinger T, Haberland U, et al. Quantitative whole heart stress perfusion CT imaging as noninvasive assessment of hemodynamics in coronary artery stenosis: preliminary animal experience. *Invest Radiol* 2010;45:298-305.
 27. Bamberg F, Becker A, Schwarz F, Marcus RP, Greif M, von Ziegler F, et al. Detection of hemodynamically significant coronary artery stenosis: incremental diagnostic value of dynamic CT-based myocardial perfusion imaging. *Radiology* 2011;260:689-698.
 28. Kitagawa K, George RT, Arbab-Zadeh A, Lima JA, Lardo AC. Characterization and correction of beam-hardening artifacts during dynamic volume CT assessment of myocardial perfusion. *Radiology* 2010;256:111-118.
 29. Stenner P, Schmidt B, Allmendinger T, Flohr T, Kachelrie M. Dynamic iterative beam hardening correction (DIBHC) in myocardial perfusion imaging using contrast-enhanced computed tomography. *Invest Radiol* 2010;45:314-323.
 30. So A, Imai Y, Nett B, Jackson J, Nett L, Hsieh J, et al. Technical note: evaluation of a 160-mm/256-row CT scanner for whole-heart quantitative myocardial perfusion imaging. *Med Phys* 2016;43:4821.
 31. Tao Y, Chen GH, Hacker TA, Raval AN, Van Lysel MS, Speidel MA. Low dose dynamic CT myocardial perfusion imaging using a statistical iterative reconstruction method. *Med Phys* 2014;41:071914.
 32. Gramer BM, Muenzel D, Leber V, von Thaden AK, Feussner H, Schneider A, et al. Impact of iterative reconstruction on CNR and SNR in dynamic myocardial perfusion imaging in an animal model. *Eur Radiol* 2012;22:2654-2661.
 33. Pelgrim GJ, Handayani A, Dijkstra H, Prakken NH, Slart RH, Oudkerk M, et al. Quantitative myocardial perfusion with dynamic contrast-enhanced imaging in MRI and CT: theoretical models and current implementation. *Biomed Res Int* 2016;2016:1734190.
 34. Bindschadler M, Modgil D, Branch KR, La Riviere PJ, Alessio AM. Comparison of blood flow models and acquisitions for quantitative myocardial perfusion estimation from dynamic CT. *Phys Med Biol* 2014;59:1533-1556.
 35. Ishida M, Kitagawa K, Ichihara T, Natsume T, Nakayama R, Nagasawa N, et al. Underestimation of myocardial blood flow by dynamic perfusion CT: explanations by two-compartment model analysis and limited temporal sampling of dynamic CT. *J Cardiovasc Comput Tomogr* 2016;10:207-214.
 36. Ishida M, Ichihara T, Nagata M, Ishida N, Takase S, Kurita T, et al. Quantification of myocardial blood flow using model based analysis of first-pass perfusion MRI: extraction fraction of Gd-DTPA varies with myocardial blood flow in human myocardium. *Magn Reson Med* 2011;66:1391-1399.
 37. Bamberg F, Hinkel R, Schwarz F, Sandner TA, Baloch E, Marcus R, et al. Accuracy of dynamic computed tomography adenosine stress myocardial perfusion imaging in estimating myocardial blood flow at various degrees of coronary artery stenosis using a porcine animal model. *Investigative Radiology* 2012;47:71-77.
 38. Pelgrim GJ, Das M, van Tuijl S, van Assen M, Prinzen FW, Stijnen M, et al. Validation of myocardial perfusion quantification by dynamic CT in an ex-vivo porcine heart model. *Int J Cardiovasc Imaging* 2017;33:1821-1830.
 39. Rossi A, Uitterdijk A, Dijkshoorn M, Klotz E, Dharampala A, van Straten M, et al. Quantification of myocardial blood flow by adenosine-stress CT perfusion imaging in pigs during various degrees of stenosis correlates well with coronary artery blood flow and fractional flow reserve. *Eur Heart J Cardiovasc Imaging* 2013;14:331-338.
 40. Pelgrim GJ, Duguay TM, Stijnen JM, Varga-Szemes A, Van Tuijl S, Schoepf UJ, et al. Analysis of myocardial perfusion parameters in an ex-vivo porcine heart model using third generation dual-source CT. *J Cardiovasc Comput Tomogr* 2017;11:141-147.

41. Schwarz F, Hinkel R, Baloch E, Marcus RP, Hildebrandt K, Sandner TA, et al. Myocardial CT perfusion imaging in a large animal model: comparison of dynamic versus single-phase acquisitions. *JACC Cardiovasc Imaging* 2013;6:1229-1238.
42. Bastarrika G, Ramos-Duran L, Rosenblum MA, Kang DK, Rowe GW, Schoepf UJ. Adenosine-stress dynamic myocardial CT perfusion imaging: initial clinical experience. *Invest Radiol* 2010;45:306-313.
43. Weininger M, Schoepf UJ, Ramachandra A, Fink C, Rowe GW, Costello P, et al. Adenosine-stress dynamic real-time myocardial perfusion CT and adenosine-stress first-pass dual-energy myocardial perfusion CT for the assessment of acute chest pain: initial results. *Eur J Radiol* 2012;81:3703-3710.
44. Kim SM, Choi JH, Chang SA, Choe YH. Detection of ischaemic myocardial lesions with coronary CT angiography and adenosine-stress dynamic perfusion imaging using a 128-slice dual-source CT: diagnostic performance in comparison with cardiac MRI. *Br J Radiol* 2013;86:20130481.
45. Bamberg F, Marcus RP, Becker A, Hildebrandt K, Bauner K, Schwarz F, et al. Dynamic myocardial CT perfusion imaging for evaluation of myocardial ischemia as determined by MR imaging. *JACC Cardiovasc Imaging* 2014;7:267-277.
46. Ho KT, Chua KC, Klotz E, Panknin C. Stress and rest dynamic myocardial perfusion imaging by evaluation of complete time-attenuation curves with dual-source CT. *JACC Cardiovasc Imaging* 2010;3:811-820.
47. Wang Y, Qin L, Shi X, Zeng Y, Jing H, Schoepf UJ, et al. Adenosine-stress dynamic myocardial perfusion imaging with second-generation dual-source CT: comparison with conventional catheter coronary angiography and SPECT nuclear myocardial perfusion imaging. *AJR Am J Roentgenol* 2012;198:521-529.
48. Greif M, von Ziegler F, Bamberg F, Tittus J, Schwarz F, D'Anastasi M, et al. CT stress perfusion imaging for detection of haemodynamically relevant coronary stenosis as defined by FFR. *Heart* 2013;99:1004-1011.
49. Kono AK, Coenen A, Lubbers M, Kurata A, Rossi A, Dharampal A, et al. Relative myocardial blood flow by dynamic computed tomographic perfusion imaging predicts hemodynamic significance of coronary stenosis better than absolute blood flow. *Invest Radiol* 2014;49:801-807.
50. Rossi A, Dharampal A, Wragg A, Davies LC, van Geuns RJ, Anagnostopoulos C, et al. Diagnostic performance of hyperaemic myocardial blood flow index obtained by dynamic computed tomography: does it predict functionally significant coronary lesions? *Eur Heart J Cardiovasc Imaging* 2014;15:85-94.
51. Coenen A, Rossi A, Lubbers MM, Kurata A, Kono AK, Chelu RG, et al. Integrating CT myocardial perfusion and CT-FFR in the work-up of coronary artery disease. *JACC Cardiovasc Imaging* 2017;10:760-770.
52. Coenen A, Lubbers MM, Kurata A, Kono A, Dedic A, Chelu RG, et al. Diagnostic value of transmural perfusion ratio derived from dynamic CT-based myocardial perfusion imaging for the detection of haemodynamically relevant coronary artery stenosis. *Eur Radiol* 2017;27:2309-2316.
53. Goto Y, Kitagawa K, Uno M, Nakamori S, Ito T, Nagasawa N, et al. Diagnostic accuracy of endocardial-to-epicardial myocardial blood flow ratio for the detection of significant coronary artery disease with dynamic myocardial perfusion dual-source computed tomography. *Circ J* 2017;81:1477-1483.
54. Danad I, Rajmakers PG, Appelman YE, Harms HJ, de Haan S, van den Oever ML, et al. Coronary risk factors and myocardial blood flow in patients evaluated for coronary artery disease: a quantitative ^{15}O H₂O PET/CT study. *Eur J Nucl Med Mol Imaging* 2012;39:102-112.
55. Liga R, Rovai D, Sampietro T, Vecoli C, Todiere G, Caselli C, et al. Insulin resistance is a major determinant of myocardial blood flow impairment in anginal patients. *Eur J Nucl Med Mol Imaging* 2013;40:1905-1913.
56. Chareonthaitawee P, Kaufmann PA, Rimoldi O, Camici PG. Heterogeneity of resting and hyperemic myocardial blood flow in healthy humans. *Cardiovasc Res* 2001;50:151-161.
57. Gould KL, Kirkeeide RL, Buchi M. Coronary flow reserve as a physiologic measure of stenosis severity. *J Am Coll Cardiol* 1990;15:459-474.
58. Kim EY, Chung WJ, Sung YM, Byun SS, Park JH, Kim JH, et al. Normal range and regional heterogeneity of myocardial perfusion in healthy human myocardium: assessment on dynamic perfusion CT using 128-slice dual-source CT. *Int J Cardiovasc Imaging* 2014;30 Suppl 1:33-40.
59. Ho KT, Ong HY, Tan G, Yong QW. Dynamic CT myocardial perfusion measurements of resting and hyperaemic blood flow in low-risk subjects with 128-slice dual-source CT. *Eur Heart J Cardiovasc Imaging* 2015;16:300-306.
60. Fujita M, Kitagawa K, Ito T, Shiraishi Y, Kurobe Y, Nagata M, et al. Dose reduction in dynamic CT stress myocardial perfusion imaging: comparison of 80-kV/370-mAs and 100-kV/300-mAs protocols. *Eur Radiol* 2014;24:748-755.
61. Kim SM, Kim YN, Choe YH. Adenosine-stress dynamic myocardial perfusion imaging using 128-slice dual-source CT: optimization of the CT protocol to reduce the radiation dose. *Int J Cardiovasc Imaging* 2013;29:875-884.
62. Lin L, Wang Y, Yi Y, Cao J, Kong L, Qian H, et al. Application of the low-dose one-stop-shop cardiac CT protocol with third-generation dual-source CT. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2017;39:34-41.
63. Ho KT, Panknin C. CT myocardial perfusion imaging of myocardial blood flow reserve before and after coronary artery stenting. *J Cardiovasc Comput Tomogr* 2011;5:125-126.
64. Danad I, Uusitalo V, Kero T, Saraste A, Rajmakers PG, Lammertsma AA, et al. Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease: cutoff values and diagnostic accuracy of quantitative $[(15)\text{O}]\text{H}_2\text{O}$ PET imaging. *J Am Coll Cardiol* 2014;64:1464-1475.
65. Kajander SA, Joutsiniemi E, Saraste M, Pietila M, Ukkonen H, Saraste A, et al. Clinical value of absolute quantification of myocardial perfusion with $(15)\text{O}$ -water in coronary artery disease. *Circ Cardiovasc Imaging* 2011;4:678-684.
66. Gupta A, Taqueti VR, van de Hoef TP, Bajaj NS, Bravo PE, Murthy VL, et al. Integrated noninvasive physiological assessment of coronary circulatory function and impact on cardiovascular mortality in patients with stable coronary artery disease. *Circulation* 2017;136:2325-2336.
67. Kurobe Y, Kitagawa K, Ito T, Kurita Y, Shiraishi Y, Nakamori S, et al. Myocardial delayed enhancement with dual-source CT: advantages of targeted spatial frequency filtration and image averaging over half-scan reconstruction. *J Cardiovasc Comput Tomogr* 2014;8:289-298.
68. Aikawa T, Oyama-Manabe N, Naya M, Ohira H, Sugimoto A, Tsujino I, et al. Delayed contrast-enhanced computed tomography in patients with known or suspected cardiac sarcoidosis: a feasibility study. *Eur Radiol* 2017;27:4054-4063.
69. Tanabe Y, Kido T, Kurata A, Kouchi T, Fukuyama N, Yokoi T, et al. Late iodine enhancement computed tomography with image subtraction for assessment of myocardial infarction. *Eur Radiol* 2018;28:1285-1292.
70. Kurita Y, Kitagawa K, Kurobe Y, Nakamori S, Nakajima H, Dohi K, et al. Estimation of myocardial extracellular volume fraction with cardiac CT in subjects without clinical coronary artery disease: a feasibility study. *J Cardiovasc Comput Tomogr* 2016;10:237-241.
71. Lee H-J, Im DJ, Youn J-C, Chang S, Suh YJ, Hong YJ, et al. Myocardial extracellular volume fraction with dual-energy equilibrium contrast-enhanced cardiac CT in nonischemic cardiomyopathy: a prospective comparison with cardiac MR imaging. *Radiology* 2016;280:49-57.