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 morphological 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
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 unnecessary radiation exposure.

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

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

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, Ktrans 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 hyperperfusion than visual assessment of dynamic CTP 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 ⁴⁰K-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-
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.
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 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].

**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.

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

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>CT scanner</th>
<th>Subjects</th>
<th>Age (yr)</th>
<th>MBF stress</th>
<th>MBF rest</th>
<th>Perfusion reserve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al.</td>
<td>19</td>
<td>Flash</td>
<td>Healthy volunteers</td>
<td>33–60</td>
<td>173±33</td>
<td>83±21</td>
<td>2.20±0.53</td>
</tr>
<tr>
<td>Ho et al.</td>
<td>35</td>
<td>Flash</td>
<td>Low-risk individuals</td>
<td>25–64</td>
<td>135±29</td>
<td>74±16</td>
<td>1.86±0.38</td>
</tr>
</tbody>
</table>

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


