Myocardial perfusion imaging using computed tomography: Current status, clinical value and prognostic implications

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ABSTRACT

Combined anatomical and functional evaluation of coronary artery disease (CAD) using computed tomography (CT) has recently emerged as an accurate, robust, and non-invasive tool for the evaluation of ischemic heart disease. Cardiac CT has become a one-stop-shop imaging modality that allows the simultaneous depiction, characterization, and quantification of coronary atherosclerosis and the assessment of myocardial ischemia. Advancements in scanner technology (improvements in spatial and temporal resolution, dual-energy imaging, wide detector panels) and the implementation of iterative reconstruction algorithms enables the detection of myocardial ischemia in both qualitative and quantitative fashion using low-dose scanning protocols. The addition of CT perfusion (CTP) to standard coronary CT angiography is a reliable tool to improve diagnostic accuracy. CTP using static first-pass imaging enables qualitative assessment of the myocardial tissue, whereas dynamic perfusion imaging can also provide quantitative information on myocardial blood flow. Myocardial tissue assessment by CTP holds the potential to refine risk in stable chest pain or microvascular dysfunction. CTP can aid the detection of residual ischemia after coronary intervention. Comprehensive evaluation of CAD using CTP might therefore improve the selection of patients for aggressive secondary prevention therapy or coronary revascularization with high diagnostic certainty. In addition, prognostic information provided by perfusion CT imaging could improve patient outcomes by quantifying the ischemic burden of the left ventricle. The current review focuses on the clinical value of myocardial perfusion imaging by CT, current status of CTP imaging and the use of myocardial CTP in various patient populations for the diagnosis of ischemic heart disease.

KEYWORDS

myocardial CT perfusion, cardiac CT, ischemic heart disease

Introduction

The evaluation of symptomatic patients suggestive of myocardial ischemia is fundamental challenge in clinical care. The use of functional imaging in cardiology has led to a high number of unnecessary catheterizations with no obstructive disease [1]. On the other hand, anatomical evaluation by using coronary computed tomography angiography (CTA) has emerged as a reliable and accurate diagnostic tool for the evaluation of coronary artery disease (CAD) [2, 3]. Due to its high sensitivity and negative predictive value it is an accurate tool to rule out CAD in patients with low-to intermediate risk of obstructive disease [4, 5], however finding the proper test for the assessment of patients with suspected CAD without generating unnecessary downstream testing and to guide patient management is challenging.

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Limitations of coronary CTA include that it tends to overestimate the severity of stenosis especially in the case of intermediate to severe lumen stenosis, multivessel disease, and extensive calcification, consequently lowering its specificity and positive predictive value. CT perfusion (CTP) imaging has emerged as a robust tool to complement traditional anatomical assessment of CAD by CTA. CTP imaging has the potential to also improve diagnosis in patients with higher likelihood of CAD or with microvascular disease and to detect residual ischemia after percutaneous coronary intervention. Current review focuses on the clinical value of myocardial perfusion imaging by CT, current status of CTP imaging and the use of myocardial CTP in various patient populations for the diagnosis of ischemic heart disease.

Coronary CTA for the evaluation of stable chest pain: current status

In the 2019 European Society of Cardiology guidelines CTA received class I recommendation for the evaluation of chronic coronary syndrome in patients with stable symptoms [6]. Two main studies were performed to underline the pivotal role of anatomical testing using CTA for stable angina. The results of the randomized SCOT-HEART (Scottish Computed Tomography of the Heart, NCT01149590) trial have shown that CTA based patient management could substantially improve long term outcomes as compared to standard care alone [7]. The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain, NCT01174550) trial has evaluated 10,003 symptomatic patients who were randomized either to functional or anatomical strategy to prove that CTA is non-inferior to functional testing [8]. Although the trial found no difference in the primary outcome, it did emphasize the prognostic value of CTA findings. Importantly, CTA also permits the detection of prognostically relevant non-obstructive CAD (between 1 and 69% luminal narrowing) that has been identified as an important predictor of adverse cardiac events [9]. Anatomical assessment using CTA provided better prognostic information as compared with functional testing that resulted also from the indiscriminatory nature of ischemia testing.

Despite its excellent capability to detect atherosclerotic plaque burden, the physiologic significance of the identified lesions remains unknown. In the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation, NCT00267774) study combining anatomical and functional evaluation (invasive measurement of lesion specific ischemia) of patients with suspected CAD improved clinical outcome [10]. Similarly, the combination of coronary CTA and CT perfusion imaging can improve diagnostic accuracy and proper identification of patients who require revascularization. The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches, NCT01471522) trial further improved our

understanding on the management of patients with stable angina and proven ischemia [11]. Optimal medical therapy proved to be non-inferior to percutaneous intervention for adverse events, although latter could improve symptoms of angina. Notably, in the ISCHEMIA trial anatomical severity of CAD increased risk for adverse events, whereas proven ischemia did not.

CT perfusion imaging for the detection of myocardial ischemia

As an anatomical imaging test, traditional coronary CTA does not allow the detection of myocardial ischemia. Physiological evaluation of CAD is of utmost importance for patient management since ischemia driven revascularization could provide better outcomes [12–15]. Also, there is a remarkable discrepancy between luminal stenosis and detectable ischemia by either single-photon emission computed tomography (SPECT) or invasive fractional flow reserve (FFR). In the RICPORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain? NCT01070771) study after visual assessment of coronary stenosis by invasive coronary angiography (ICA), additional FFR measurement changed patient management in one-quarter of patients with stable angina [16]. Similarly, only 50% of patients with obstructive CAD on CTA had abnormal perfusion parameters assessed with SPECT [17].

Patients with less than 30% stenosis would possibly not benefit from ischemia testing, whereas lesions above 80% stenosis proved to be predominantly hemodynamically relevant [18]. Notably, revascularization does not improve symptoms or outcome in patients with no detectable ischemia, whereas some evidence suggests that more than 10% ischemia is associated with better prognosis after revascularization [19].

Functional testing includes stress echocardiography, stress magnetic resonance imaging (MRI), SPECT or positron-emission tomography (PET) imaging based on local expertise and accessibility. CTP imaging was introduced as a new-comer modality for ischemia detection. CTP is able to detect hypo-attenuated areas corresponding to myocardial injury in the left ventricle (LV) during first-pass of the contrast agent (see [Central illustration](#)). Advancements in CT scanner technology led to an improved spatial and temporal resolution with lower radiation exposure and contrast agent use by implementing iterative reconstruction algorithms. Also, wide detector CT scanners provide complete coverage (up to 16 cm z-axis coverage) of the heart volume. Rest CTA images are performed either as first to rule out CAD with subsequent ischemia provocation using vasodilator stressor agents (predominantly adenosine and regadenoson) or after stress imaging to avoid pre-enhancement of the myocardial tissue [20]. There are no guidelines on the exact order of stress and rest imaging, however in general it is recommended to start with a rest scan for lower

Central illustration. The addition of CTP to CCTA for the detection of hemodynamically relevant coronary lesions. Representative case of a patient presenting with stable chest pain. Panel left: CTA image of the left anterior descending (LAD) with high-grade stenosis in the proximal segment (white arrow). Panel middle: Dynamic CTP image showing hypoattenuated regions in the mid-anterior and mid-antero-septal segments of the left ventricle. Panel right: ICA shows significant stenosis in LAD (white arrow). CCTA: coronary CT angiography; CTA: CT angiography; CTP: CT perfusion; DPCT: dynamic perfusion CT; ICA: invasive coronary angiography; LAD: left anterior descending

risk patients, and conversely, an initial stress scan should be performed for higher risk patients based on traditional risk scores and/or coronary calcium scoring. Notably, different stressor agents are in use to provoke ischemia during the CT scan. Recent investigations used regadenoson – a selective A2A agonist – in a single 10 second bolus that can be used in the same intravenous line as for the contrast injection [21]. Regadenoson provides adequate long and effective vasodilator stress for CTP and can be safely used without dose modulations for patients' size or co-morbidities [22].

Currently two different acquisitions are available to perform CTP with the aim to diagnose perfusion abnormalities through the myocardial tissue: static and dynamic myocardial perfusion CT. Furthermore, static stress CTP imaging can be performed using monoenergetic or dual-energy CT acquisition, where rest images are derived from the coronary CTA. Static CTP shows the peak blood flow of the myocardium (myocardial blood flow in one specific timepoint) allowing qualitative and semi-quantitative analysis of myocardial perfusion (Fig. 1). Therefore, the optimal timing for static CTP is crucial [20, 23]. Investigations demonstrated that dual-energy perfusion imaging using iodine mapping improves the detection of ischemia as compared to monoenergetic static CTP [24, 25]. On the other hand, dynamic CTP (usually stress imaging only) depicts contrast distribution in the LV wall during several cardiac cycles in order to obtain time attenuation curves (TACs) and the arterial input function curve (upslope method) to calculate myocardial blood flow. TAC curves for normal and ischemic myocardial segments differ markedly

[26] (Fig. 2). It therefore also enables assessment of semi-quantitative and quantitative parameters of myocardial perfusion such as the upslope, peak enhancement, time to peak (TTP), area under the curve, absolute, and relative myocardial blood flow (MBF) values, and myocardial blood volume (MBV). Dynamic stress CTP also allows for more precise and reproducible detection of balanced ischemia in multivessel disease as compared with static CTP. Although growing body of evidence suggest the improved diagnostic accuracy of CTP using dynamic stress perfusion protocols with quantitative assessment, this method is associated with increased radiation exposure (approx. 4–15 mSv) [20, 27]. Importantly, wide variability exists in both the imaging protocols and the cut-off values of perfusion parameters for discriminating ischemic myocardial segments. Previous studies reported a wide range of MBF thresholds for the detection of myocardial ischemia from 75 to even 103 mL/100 mL/min measured using a region of interest in a given segment [27–35]. Also, data are limited on the prognostic value of quantitative CTP parameters. Vendor specific technical aspects of CTP protocols are summarized in prior publications [18, 20, 24, 36]. Detailed description of technical aspects and outcomes are summarized in Table 1.

Earlier this year, the Society of Cardiovascular Computed Tomography (SCCT) released a consensus document on myocardial perfusion imaging [37]. This long-anticipated document summarizes the technical principles, diagnostic value, patient selection, image acquisition and interpretation of CTP imaging and also defines the key elements of reporting the results for the referring physician. Notably, the

Fig. 1. Static CT perfusion imaging for detecting hemodynamically significant CAD in patients with stable chest pain and intermediate lesion. Representative images of a patient presenting with stable chest pain. Static CT perfusion allows for the visual assessment (qualitative or semi-quantitative) of perfusion defects. Panel left: CCTA image of the right coronary artery (RCA) with moderate stenosis in the proximal segment (white arrow). Panel middle: Rest and stress static CTP images. No perfusion defect was observed on the rest CT scan, while hypoattenuated regions in the mid-inferior and mid-inferoseptal segments of the left ventricular wall were present under stress (black arrows). Panel right: ICA shows significant stenosis in the proximal RCA with an invasive FFR value of 0.72 (black arrow). CAD: coronary artery disease; CCTA: coronary CT angiography; CTA: CT angiography; CTP: CT perfusion; FFR: fractional flow reserve; ICA: invasive coronary angiography; RCA: right coronary artery

Fig. 2. Dynamic CT perfusion for the detection of myocardial ischemia. Dynamic CT perfusion enables the quantification of myocardial hemodynamics during stress. TAC curves are generated for the aorta and the selected myocardial segments. The red region of interest (ROI) represents the mid-inferolateral segment, whereas the green ROI stands for the mid-inferoseptal segment. Substantial differences are observed in the TAC curves and CTP revealed perfusion deficit of the inferolateral wall (reduced MBF values of 61 mL/100 mL/min in the inferolateral and normal perfusion of 143 mL/100 mL/min in the inferoseptal segment). CTP: CT perfusion; HU: Hounsfield unit; MBF: myocardial blood flow; TAC: time attenuation curve; ROI: region of interest

Table 1. Technical aspects and main outcomes of static and dynamic CTP studies

Author, year	Patient number	CT scanner	Stress agent	Analysis	Reference standard	Radiation dose of CTP (mSv)	Outcome
Static CTP							
Bettencourt et al. [70]	101	64-slice	Adenosine	Visual	FFR, MRI	5.0*	CTA + CTP for detecting significant CAD: SE: 90%; SP: 81%; PPV: 80%; NPV: 90%
Rochitte et al. [71]	381	320-slice	Adenosine	Semi-quantitative	SPECT	5.31	CTA + CTP: SE: 80%; SP: 74%; PPV: 65%; NPV: 86%
Cury et al. [43]	110	Multivendor	Regadenoson	Semi-quantitative	SPECT	17.70*	CTP was non-inferior; agreement rate: 0.87; SE: 90%; SP: 84%
Pontone et al. [46]	147	256-slice	Adenosine	Visual	FFR	2.5	CCTA + CTP patient based SE: 98%; SP: 87%; NPV: 99%; PPV: 86%
Andreini et al. [72]	150	256-slice	Adenosine	Visual	QCA	2.26	Highest diagnostic accuracy using CTP + CTA 95.8% in the territory-based analysis
Static dual-energy CTP							
Delgado et al. [73]	56	DS 2G	Adenosine	Iodine map	MRI	5.2	SE: 76%; SP: 99%; PPV: 89%; NPV: 98% per segment analysis
Meinel et al. [74]	55	DS 2G	Adenosine	Iodine map	SPECT	7.1	SE: 99%; SP: 97%; PPV: 92%; NPV: 100% per segment analysis
Kim et al. [75]	50	DS 2G	Adenosine	Iodine map	MRI	6.5	SE: 77%; SP: 94%; PPV: 53%; NPV: 98% per segment analysis
Ko et al. [76]	100	DS 1G	Adenosine	Iodine map	QCA + MRI	4.2	SE: 87%; SP: 79%; PPV: 71%; NPV: 91% vessel based analysis
Sánchez-Gracián et al. [77]	36	DS 2G	Adenosine	Iodine map	MRI	5.42	Threshold: 2.1 mg/mL; SE: 75%; SP: 73.6%
Dynamic CTP							
Bamberg et al. [30]	31	DS 2G	Adenosine	Quantitative	MRI	11.08	Estimated MBF threshold for perfusion defect 88 mL/mg/min; SE: 77.8%; SP: 75.4%; PPV: 50.6%; NPV: 91.3%
Rossi et al. [29]	80	DS 2G	Adenosine	Quantitative	FFR	9.4	78 mL/100 mL/min cut-off value for MBF index; SP was 89% for intermediate lesions
Coenen et al. [32]	74	DS 3G	Adenosine	Quantitative	ICA/FFR	9.3	CT MPI (indexed MBF) and CT-FFR had comparable accuracy
Nishiyama et al. [78]	38	256-slice	Adenosine	Quantitative	ICA/FFR	10.2	MBF cutoff 1.26 mL/g/min for detecting obstructive CAD
Yi et al. [79]	60	DS 3G	Adenosine	Quantitative	ICA/FFR	NA	Relative MBF ratio with highest segmental MBF provided optimal diagnostic accuracy (versus average and 3rd quartile segmental MBF)
Yang et al. [80]	82	DS 2G	Adenosine	Quantitative	ICA/FFR	3.5	AUC was 0.91 for the combination of stenosis $\geq 50\%$ by CTA and SFR (ratio of hyperemic MBF in a stenosed artery versus in a non-diseased artery)
Pontone et al. [28]	85	256-slice	Adenosine	Quantitative	ICA/FFR	5.3	The sequential strategy of CCTA + FFRCT + CTP showed the highest AUC (0.919; $P < 0.05$) as compared with all other strategies. Threshold for absolute MBF 101 mL/100 g/min
Alessio et al. [81]	34	256-slice	Regadenoson	Quantitative	PET	8.4	Global MBF highly correlated with PET ($r = 0.92$; $P < 0.001$); mean difference: $0.7 \pm 26.4\%$
Yi et al. [82]	60	DS 3G	Adenosine	Quantitative	ICA/FFR	NA	Absolute MBF value was superior than relative MBF ratio (AUC:0.955 versus 0.906 $P = 0.02$); cut-off for absolute MBF:115.7 mL/100 mL/min
Li et al. [83]	62	DS 3G	Adenosine	Quantitative	FFR	3.0	AUC: 0.942 for absolute MBF and AUC: 0.956 for relative MBF lesion based analysis

*Radiation dose for both rest and stress CTA.

1G: first-generation scanner; 2G: second-generation scanner; 3G: third-generation scanner; AUC: area under the curve; CAD: coronary artery disease; CTA: CT angiography; CCTA: coronary CT angiography; CTP: CT perfusion; DS: dual-source scanner; FFR: fractional flow reserve; MBF: myocardial blood flow; MPI: myocardial perfusion imaging; MRI: magnetic resonance imaging; mSv: millisievert; NA: non-assessable; NPV: negative predictive value; PET: positron emission tomography; PPV: positive predictive value; QCA: quantitative coronary angiography; SE: sensitivity; SFR: stress myocardial blood flow ratio; SP: specificity; SPECT: single-photon emission computed tomography.

consensus document encourages the use of CTP in patients with high likelihood of ischemic heart disease, known CAD, prior coronary intervention or extensive calcification.

Diagnostic performance of different CTP imaging protocols

CTP is an emerging technology that was developed to improve the diagnostic performance of coronary CTA. In single center studies CTP had excellent diagnostic performance compared to SPECT, CMR, PET, ICA, and invasive FFR [38–41]. In the CORE320 (Combined Non-invasive Coronary Angiography and Myocardial Perfusion Imaging Using 320 Detector Computed Tomography, NCT00934037) multicenter study static stress myocardial CTP and SPECT perfusion were compared in patients with known significant CAD detected by ICA and found higher overall diagnostic performance for static CTP [42]. In another multicenter study Cury et al. found that CTP was non-inferior to SPECT in the detection of reverse myocardial ischemia [43]. According to the meta-analysis of Takx et al., CTP had a pooled sensitivity and specificity of 88 and 80% using ICA with FFR as reference standard [44]. Furthermore, the diagnostic performance of CTP was similar to PET and stress MRI and higher than SPECT and echocardiography. A meta-analysis of CTP studies found similar diagnostic accuracy for static and dynamic techniques with a sensitivity and specificity of 82 and 78% for static and 77 and 89% for dynamic CTP. Sørgaard et al. in their meta-analysis found that compared to coronary CTA alone, combining CTP, and coronary CTA improved specificity from 62 to 84% when using ICA as reference standard [45]. CTP is therefore a promising and accessible tool that has superior spatial resolution as compared with SPECT to detect even smaller territories of myocardial ischemia. While there are several alternative, extensively validated modalities to provide functional information on CAD, CT is the only non-invasive modality for the combined assessments of morphology and function to guide patient management.

The PERFECTION (Comparison Between Stress Cardiac Computed Tomography Perfusion Versus Fractional Flow Reserve Measured by Computed Tomography Angiography In the Evaluation of Suspected Coronary Artery Disease) prospective study aimed to compare the diagnostic accuracy of CTA with combined CTA + CT-FFR and CTA + static stress-CTP in detecting functionally significant CAD using invasive FFR as the reference standard. The study enrolled 147 consecutive symptomatic patients, and found that complementary functional information obtained by either CT-FFR or CTP significantly improves diagnostic performance, but no significant difference was detected between CTA + CT-FFR versus CTA + CTP [46]. Even though both CT-FFR and CT + CTP yielded statistically similar diagnostic performance, combined CT and static or dynamic CTP might provide additive diagnostic value in patients with inconclusive CT-FFR due to the higher specificity and

positive predictive value [47]. CT-FFR provides information on the lesion-specific ischemia and is derived from rest CTA images therefore highly dependent on image quality. Dynamic CTP on the other hand could quantify total myocardial burden and thus might be useful in patients with extensive CAD or microvascular disease.

Growing body of evidence suggests that using CT for the detection of myocardial perfusion defects is feasible and reliable compared to other non-invasive and invasive methods. However, the lack of standardized methods regarding image acquisition, stress protocols and particularly image analysis limits its widespread use. Moreover, there is no unified MBF cutoff value for the detection of ischemic myocardium. Although the number of CTP tests is increasing as part of routine clinical assessment of intermediate lesions, there are limited data on the clinical value of CTP in specific patient populations prone to have ischemic heart disease.

Potential role of myocardial perfusion imaging by CT in clinical practice

Studies examining the potential role of CTP in clinical practice are scarce. In the evaluation of ischemic heart disease using additional stress CTP has a higher sensitivity compared to anatomical assessment alone mainly due to the reduction of false positive findings. Therefore, CTA could become a more robust gatekeeper by reducing unnecessary invasive procedures. Table 2 summarizes the potential role of CTP for a wide spectrum of ischemic heart disease patients.

Stable angina

Myocardial perfusion imaging by CT can improve patient management in stable angina. In the multicenter prospective CRESCENT-II (Comprehensive Cardiac CT Versus Exercise Testing in Suspected Coronary Artery Disease 2, NCT02291484) trial a diagnostic pathway including CTP was compared with traditional functional testing in patients with stable chest pain and found to be an effective and safe alternative for the diagnosis of CAD by lowering rates of ICA without coronary revascularization [48]. Similarly, in another study including 240 consecutive patients, adding dynamic CTP to CTA significantly reduced the number of unnecessary invasive testing in patients with intermediate risk for CAD (CTA only: 50.0% [29/58] versus CTA + CTP: 10.8% [4/37], $P < 0.0001$) [49]. Myocardial ischemia was determined as $MBF \leq 100 \text{ mL}/100 \text{ mL}/\text{min}$. In addition, van Rosendael et al. found a five-fold reduction of performing ICA in patients with obstructive CAD in case of normal myocardial perfusion on static stress CTP images [50].

Patients with extensive coronary calcification detected on native CT scans could be an optimal target for stress CTP. In challenging cases such as severe calcification (coronary calcium score ≥ 400), combined CTA and CTP is superior to CTA alone by providing additional functional information

Table 2. Potential clinical use of CTP in the spectrum of ischemic heart disease

Potential role of CTP	
Stable angina	<p>Improve patient management in stable angina by detecting ischemic segments.</p> <p>Better gatekeeper function of FFR by reducing unnecessary invasive procedures.</p> <p>Superior spatial resolution as compared with SPECT.</p> <p>Useful in patients with extensive calcification (blooming artifacts).</p> <p>Multivessel CAD evaluation to select vessel(s) for revascularization (dynamic CTP).</p> <p>Prognostic information provided by combining plaque burden and ischemic load.</p> <p>Ischemia detection in the presence of previously implanted stents.</p> <p>Evaluation of microvascular dysfunction using parameters of myocardial tissue hemodynamics.</p>
Acute chest pain	Exclude obstructive CAD in patients with low risk for ACS.
Post-myocardial infarction	Improve risk prediction in patients after MI by evaluating infarcted territories.
Extensive non-obstructive CAD	Global ischemia detection by quantitative CTP parameters.
Diabetes mellitus and arterial hypertension	Early identification of epicardial coronary atherosclerosis, microvascular dysfunction and impaired myocardial perfusion in patients at higher risk.

ACS: acute coronary syndrome; CAD: coronary artery disease; CCTA: coronary CT angiography; CTP: CT perfusion; FFR: fractional flow reserve; MI: myocardial infarction; SPECT: single-photon emission computed tomography.

of coronary lesions (AUC = 0.97 versus AUC = 0.088, $P = 0.030$). However, in patients with high pretest probability or known CAD combining CTA and CTP did not improve diagnostic performance in case of low Agatston calcium score (coronary calcium score < 400) [51].

More recent studies also examined the impact of MBF as assessed by dynamic CTP on clinical outcomes and found that it has an additive prognostic value over coronary CTA and is an independent predictor of major adverse cardiovascular events (MACEs). Using dynamic CTP, a summed stress score based on MBF values proved to be prognostically relevant after adjusted for obstructive CAD on CTA with hazard ratio (HR) of 5.7 (CI: 1.9–16.9, $P = 0.002$) [52]. Also, myocardial perfusion defect defined by low index-MBF (<0.88) calculated as a ratio between each segment and global MBF values was associated with MACE after adjusting for coronary CTA, CT-FFR findings, age, sex, and risk factors (HR: 10.1, CI: 2.1–48.8, $P = 0.004$) [53]. Notably, dynamic CTP derived perfusion parameters had additive prognostic value beyond clinical risk factors and stenosis severity assessed by coronary CTA [54]. Moreover, the extent of myocardial perfusion defect was also a prognosticator of MACE.

Currently, two large, randomized trials aimed to evaluate the clinical utility and prognostic value of CTP. The CTP-PRO (Impact of Stress Cardiac Computed Tomography Myocardial Perfusion on Downstream Resources and Prognosis in Patients with Suspected or Known Coronary Artery Disease, NCT03976921) study is an international, multicenter, prospective, open-label, randomized trial focusing on the cost-effectiveness of combined CTA + CTP strategy versus usual care in 2,000 intermediate-high risk patients with suspected or known CAD [55]. The PERFUSE RCT (Prospective Evaluation of Myocardial Perfusion Computed Tomography Trial, NCT02208388) sought to investigate the safety and effectiveness of CTP guided revascularization versus FFR guided revascularization in 1,000 patients with suspected stable CAD.

Besides the assessment of epicardial coronary arteries, CTP allows for the detection of microvascular dysfunction, although regarding data are scarce. Coronary flow reserve can also be accurately evaluated using specific dynamic CTP protocols in rest and stress phase [56]. In a recent study, quantified MBF using dynamic CTP also appeared to be significantly lower in myocardial segments affected by microvascular obstruction and had excellent diagnostic

accuracy compared to the reference CMR data ($AUC = 0.996$, $P < 0.001$) [57].

A sub-study of the CORE320 prospective trial divided patients into 3 groups based on the presence of obstructive CAD or perfusion defect defined by either coronary CTA and CTP or ICA and SPECT. Patients with ischemia but no obstructive stenosis (INOCA) were identified using CTA and static CTP. Interestingly, higher prevalence of positive remodeling, greater total and low attenuation atheroma volume was present in the INOCA group as compared to patients without either obstructive CAD or ischemia [58].

CTP after coronary intervention

Although only few studies are available, the use of CTP could also be beneficial in patients with prior coronary intervention for detecting residual ischemia. Due to the metallic artifacts the evaluation of coronary stents by CTA is limited. Adding stress CTP to rest CTA aids the diagnosis of in-stent-restenosis and helps the identification of patients who need further intervention ($AUC = 0.82$ for CTP and CTA versus $AUC = 0.69$ for CTA alone, $P < 0.001$) [59].

Acute chest pain

For patients presenting with acute on-set chest pain with low risk for acute coronary syndrome (ACS) coronary CTA is a reliable tool to exclude obstructive CAD [60]. The use of CTA can result in decreased time to diagnosis and to discharge, however it could also drive revascularization rates higher. In the CATCH-2 (Cardiac CT in the Treatment of Acute Chest Pain 2, NCT02014311) randomized controlled trial combined CTA + CTP was compared to CTA alone for the diagnosis and treatment of ischemic heart disease. The trial included patients with acute chest pain after ACS was ruled out by standard care. The combined protocol decreased the number of further invasive examinations and helped in guiding patient management [61]. In addition, in a similar patient population visual and semi-quantitative perfusion defect assessed by static CTP was associated with MACE with a median follow-up of 19 months independently of the patient's pretest probability. For visual perfusion defect the adjusted hazard ratio was 39 (CI: 11–134, $P < 0.0001$), while for impaired perfusion based on TPR (cut-off 0.89) hazard ratio was 0.99 (CI: 0.98–0.99, $P < 0.0001$). Moreover, poor prognosis was related to cases where >10% of left ventricular myocardium was affected [62].

Post-myocardial infarction patients

It has been suggested that the evaluation of infarcted area after acute myocardial infarction (AMI) could improve risk prediction, as irreversible myocardial damage is a strong long-term prognosticator. Analyzing irreversibly damaged myocardial areas is feasible using CTP parameters [63]. Nakauchi et al. quantified MBF parameters using dynamic CTP with deconvolution analysis in patients after AMI and measured significant differences in tissue blood flow and blood volume between infarcted and non-infarcted

myocardial territories (mean MBF: 51.96 versus 108.84 mL/100 g/min, $P < 0.01$) [64]. In patients with ST-segment elevation myocardial infarction and successful revascularization Pan et al. found that MBF derived from dynamic CTP significantly and inversely correlated with peak Troponin T levels ($r = -0.682$, $P < 0.001$) and left ventricular function at 6 months ($r = 0.585$, $P = 0.001$) [65].

Extensive non-obstructive CAD

In cases of large atherosclerotic plaque burden without obstructive stenosis the assessment of ischemia by CT could help in identifying patients at highest cardiovascular risk. Meinel et al. demonstrated that dynamic CTP is suitable for the evaluation of global myocardial perfusion parameters [66]. Global MBF, MBV, and volume transfer constant (K_{trans}) were analyzed and correlated well with the severity and extent of CAD on coronary CTA and visual perfusion defects. In addition, after a follow up of 6, 12, and 18 months MBF predicted cardiovascular outcomes with a two-fold increased risk for major events in case of global MBF < 121 mL/100 mL/min [67]. Global MBF also showed incremental prognostic value over age, gender, clinical risk factors and stenosis severity on coronary CTA.

Diabetes mellitus and arterial hypertension

Dynamic CTP provides global quantification of LV myocardium that could improve early recognition of developing ischemic heart disease in different conditions such as diabetes mellitus or hypertension. Using dynamic CTP lower global perfusion values were found in patients with hypertension and diabetes mellitus with suspected CAD (hypertension versus normotension: MBV 18.5 ± 3.0 versus 19.7 ± 2.3 mL/100 mL, $P < 0.05$; diabetes versus no diabetes: MBV 17.9 ± 2.4 versus 19.4 ± 2.8 mL/100 mL, $P < 0.05$) [68]. Furthermore, longer duration of diabetes was associated with lower MBF assessed by dynamic CTP, yearly 6% additional risk was detected for decreased MBF [69]. Further larger studies are needed to establish the role of CTP in the diagnosis of common comorbidities such as diabetes and hypertension.

Conclusion and future perspectives

CTP is a promising tool for the identification of the presence and severity of perfusion abnormalities using either qualitative or quantitative analysis in patients with stable or even acute chest pain. Patients with extensive CAD and diffuse calcifications are optimal candidates to further improve the gatekeeper functionality of CTA. CTP can substantially increase the diagnostic accuracy of coronary CTA to identify possible candidates for revascularization and aggressive secondary prevention. However, differences in image acquisition protocols, image analysis, and artifacts limit the widespread clinical use of CTP. Advancements in scanner technology, post-processing software, and image reconstruction may help

overcome the limitations of CTP. Also, further studies are warranted to establish proper indications for patients, who could benefit the most from CTP imaging (i.e., patients with diabetes, post-PCI, multivessel-disease, microvascular dysfunction). Furthermore, spectral CT imaging might help detect true perfusion defects using iodine density reconstructions in the future. Also, radiomic and machine learning analysis of the left ventricle may help overcome the limitations of CTP interpretation, especially the subjectivity of visual assessment. Furthermore, radiomics and machine learning may help in identifying new imaging biomarkers of the myocardium from CTP scans which may better identify myocardial injury and assist clinical decision making.

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