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FFR_{CT} and CT perfusion: A review on the evaluation of functional impact of coronary artery stenosis by cardiac CT

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ABSTRACT

Coronary computed tomography angiography (CCTA) is at the frontline of the diagnostic strategies to detect coronary artery disease (CAD). Anatomical information have proven to be insufficient to detect hemodynamic significant epicardial stenosis. In the present invited review we discuss on FFR_{CT} and stress CTP, emerging technologies for an accurate and comprehensive evaluation of patients with suspected CAD, offering both anatomical (i.e. luminal and plaque) and functional assessment in one single technique.

1. Introduction

The Prospective trials PROMISE and SCOT-HEART have demonstrated the incremental value of coronary computed tomography angiography(CCTA) over conventional practice in investigating patients with suspected angina [1–2] Relying only of anatomical information with non-invasive or invasive coronary angiography(ICA) have proven to be insufficient to detect hemodynamic significant epicardial stenosis [3]. Basic principles, current evidence and future perspectives of FFR_{CT} and CTP, both static and dynamic, are the main topics of the present expert review, whose aim is to provide an updated overview on the functional evaluation of CAD by CCTA. Even if this is not a systematic review or a meta-analysis, in order to provide a comprehensive overview of literature on these fields, we systematically searched on PubMed using the following terms: "FFR_{CT}", "CT-derived fractional flow reserve", "myocardial CTP", "static CTP", and "dynamic CTP". Previous systematic reviews and meta-analysis were evaluated and reported, while animal studies and human studies enrolling <30 patients were excluded from the present review.

2. Fractional flow reserve derived from CT - FFR_{CT}

2.1. Technical principles

Fractional Flow Reserve (FFR) is the ratio of hyperemic flow in the presence of an epicardial stenosis to hyperemic flow in the absence of this epicardial stenosis. In clinical practice, FFR is derived from pressure i.e. the ratio of distal to proximal coronary pressures [4]. Current guidelines emphasize the role of invasive FFR to determine the functional significance of a coronary stenosis [5]. This recommendation is based on clinical benefit observed with FFR guidance in randomized clinical trials. Fractional flow reserve derived from CT (FFR_{CT}) is based on the application of computational flow dynamics to images extracted from CCTA [6–7] (Fig. 1). Three principles form the basis for the coronary blood flow simulation to calculate FFR_{CT}. First, baseline coronary flow depends on myocardial oxygen demand and resting flow can be computed accounting for myocardial territory-specific ventricular mass [8–9]. Second, the resistance of the microcirculatory bed at rest is inversely, not linearly, proportional to the size of the feeding vessel, meaning that vessels size follows to the amount of flow they carry [10]. Third, the coronary microcirculation has a predicable response to adenosine. Based

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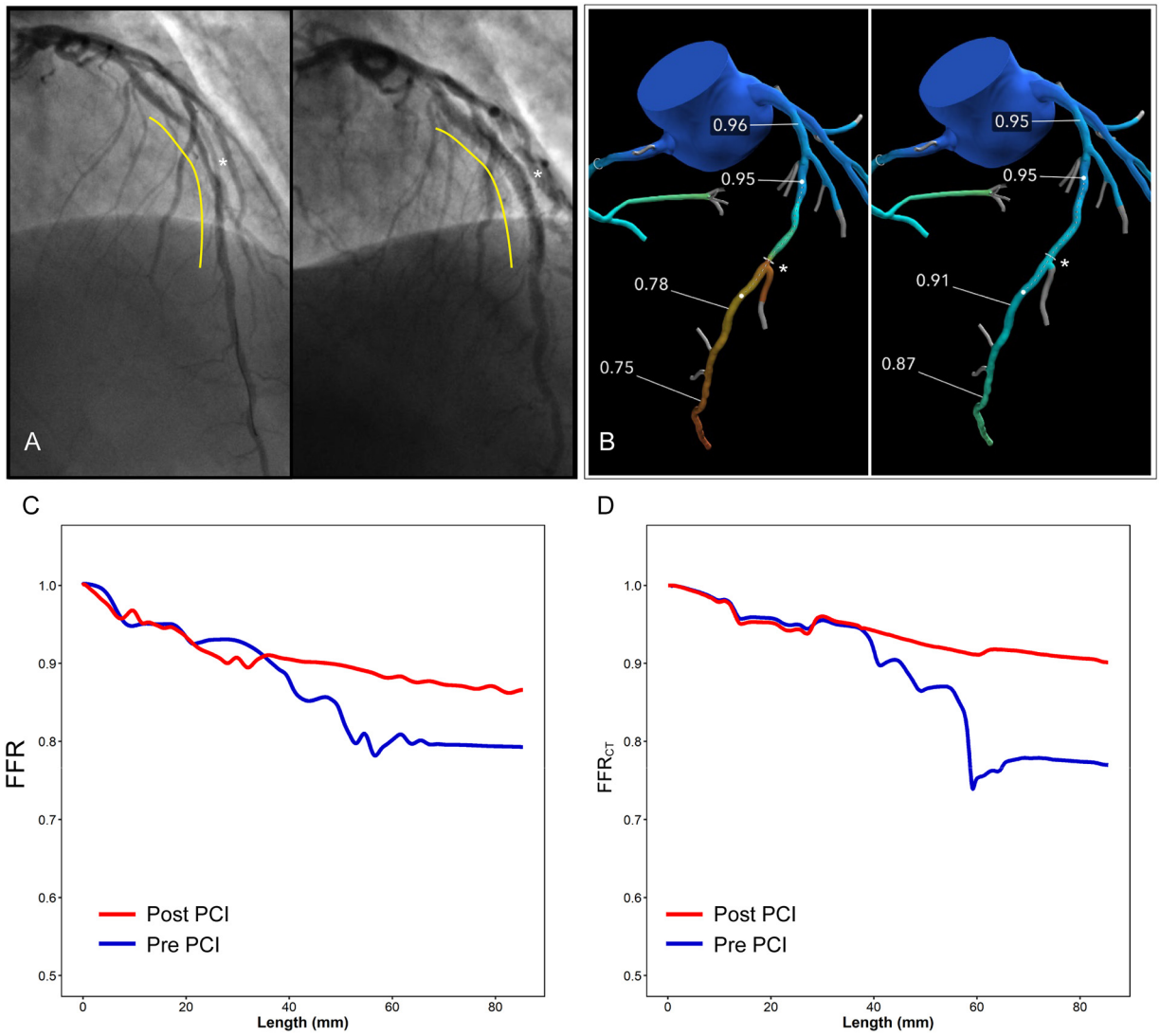

Fig. 1. Case example of invasive and non-invasive FFR pullbacks pre- and post-PCI and of the use of the HeartFlow Planner. Panel A left shows a lesion in the mid-LAD (DS 40% and lesion length 34 mm by QCA) (yellow line) and the result (A right panel) after PCI with a 3.0/38 mm stent. The HeartFlow analysis (panel B left and panel D blue line) suggested a hemodynamic significant disease with pressure drop in the mid LAD and distal FFR of 0.75. Invasive FFR confirmed a distal FFR of 0.75 (panel C blue line). Virtual PCI (panel B right) using the HeartFlow Planner enables remodellation of the luminal geometry of the diseased mid segment and recomputation of the post-PCI FFR_{CT} with a predicted, non-invasive post-PCI FFR of 0.87 (panel B right and panel D red line). Invasive FFR post-PCI reached 0.87 (panel C red line). The virtual pullback curves of FFR_{CT} pre and post-PCI with the resulting increase in vessel conductance post-PCI are depicted in panel D. In this particular case the gain in conductance was similar between non-invasive and invasive pullbacks. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

on these principles and using 3D patient-specific luminal geometries, a volumetric finite element mesh is used to simulate blood flow incorporating the fluid properties of blood. FFR_{CT} is then defined as the computed mean coronary pressure distal to a lesion divided by the mean blood pressure in the aorta under conditions of simulated maximal hyperemia [6].

2.2. Overview of the current evidence

2.2.1. Clinical validation

The studies addressing the clinical validation of FFR_{CT} are shown in Table 1. FFR_{CT} improved stenosis evaluation in terms of prediction of functional significance compared to anatomical evaluation alone. These studies used invasive FFR as standard of reference and applied similar cut-off for lesion significance (<0.80 for both modalities) [11–13]. In a recent diagnostic performance meta-analysis, FFR_{CT} showed 82% diagnostic accuracy [14]. FFR_{CT} has been tested in the broad spectrum of CAD. In three vessels CAD, the SYNTAX-II FFR_{CT} confirmed high accuracy with an AUC of 0.85(95% CI:0.79–0.9) with instantaneous wave-free ratio as a reference [15]. These studies used the Heart Flow (Redwood City, California) technology.

Recently, other approaches like on-site computed CT-fractional flow reserve (CT_{FFR}) and non- invasive instantaneous wave-free ratio using CCTA (iFR_{CT}) have been developed. Initial retrospective studies have shown moderate correlation with invasive FFR.

2.2.2. FFR_{CT}: Real-world use and safety

The PLATFORM was a pragmatic trial including stable, symptomatic patients with planned invasive or non-invasive evaluation of suspected CAD. Patients were then subdivided to be evaluated either with usual care or CCTA with FFR_{CT} as diagnostic strategy. FFR_{CT} significantly reduced the rate of ICA without obstructive CAD (73.3% vs. 12.4%, risk difference 60.8% CI 53.0–68.7%, $p < 0.001$). As such, 61% of invasive coronary angiographies showing no obstructive epicardial disease were deferred. In addition, an increasing rate of patients were revascularized based on coronary physiology (95% CCTA/FFR_{CT} vs. 55% usual care) [16]. A CCTA/FFR_{CT} diagnostic work-up reduced costs. At one year patients who were in the planned invasive test group, FFR_{CT}–

Table 1
Overview of FFR_{CT} studies.

		Sites	Regions	Study design	Population	Primary endpoint published	FFR_{CT} version used	Primary endpoint/ objective
DISCOVER-FLOW	103 pts. (159 vessels)	4	US, Korea, Latvia	Prospective	Pts with suspected or known CAD	Nov 2011 JACC	pre-1.x	To determine the diagnostic performance of noninvasively derived FFR_{CT} using invasive FFR as the gold standard
DEFACTO	252 pts. (407 vessels)	17	US, Canada, Korea, Europe	Prospective	Pts with suspected or known CAD	Aug 2012 JAMA	pre-1.x	To determine the diagnostic performance of noninvasively derived FFR_{CT} using invasive FFR as the gold standard
NXT	254 pts. (484 vessels)	10	Europe, Korea, Japan, Australia	Prospective	Pts with suspected stable CAD	Apr 2014 JACC	1.x	To determine the diagnostic performance of noninvasively derived FFR_{CT} using invasive FFR as the gold standard
PLATFORM	584 pts	11	Europe	Prospective consecutive cohort	Pts with stable chest pain, primary endpoint required planned ICA	Aug 2015 EHJ	1.x	To determine the impact of using a pathway of CTA ± FFR_{CT} instead of usual care on ICA showing no obstructive disease
RIPCORD FFR_{CT}	200 pts	11	Europe, Korea, Japan, Australia	Retrospective analysis of NXT study	Pts with suspected stable CAD	Oct 2016 JACC Imaging	1.x	To determine during a case review how management plan changes using cCTA alone compared to cCTA + FFR_{CT}
PROMISE FFR_{CT} sub study	181 analyzable cases	Analyzable cases came from 69 sites	US, Canada	Retrospective case review	Pts from the PROMISE study referred for ICA w/in 90 days of cCTA	Apr 2017 JACC Imaging	1.x	To determine if FFR_{CT} predicts revasc and outcomes and if its addition improves efficiency of referral to ICA
Syntax II sub study	77 pts	22	Europe	Subgroup analysis of a prospective study	Pts with 3 vessel disease by ICA	May 2018 JACC	1.x	To assess the feasibility of and validate the noninvasive functional SYNTAX score (FSS) derived from cCTA with FFR_{CT}
ADVANCE	5083 pts	38	US, Canada, Europe, Japan	Prospective registry	Pts with suspected stable CAD	Aug 2018 EHJ	1.x & 2.x	To determine if treatment plan changes using cCTA alone compared to cCTA + FFR_{CT}, as assessed by a core lab
Syntax III Revolution	223 pts	6	Europe	Prospective RCT	Pts with left main or 3 vessel disease by ICA	Sep 2018 EHJ	1.x & 2.x	To determine, in blinded fashion, the agreement of revascularization strategy based either on cCTA + FFR_{CT} or conventional angiography
PACIFIC FFR_{CT} sub study	208 pts	1	Europe	Retrospective analysis of a prospective study	Pts with suspected stable CAD	Jan 2019 JACC	2.x	To evaluate diagnostic performance of FFR_{CT} using invasive FFR as the gold standard, and compare to cCTA, SPECT, and $[^{15}O]H_2O$ PET.

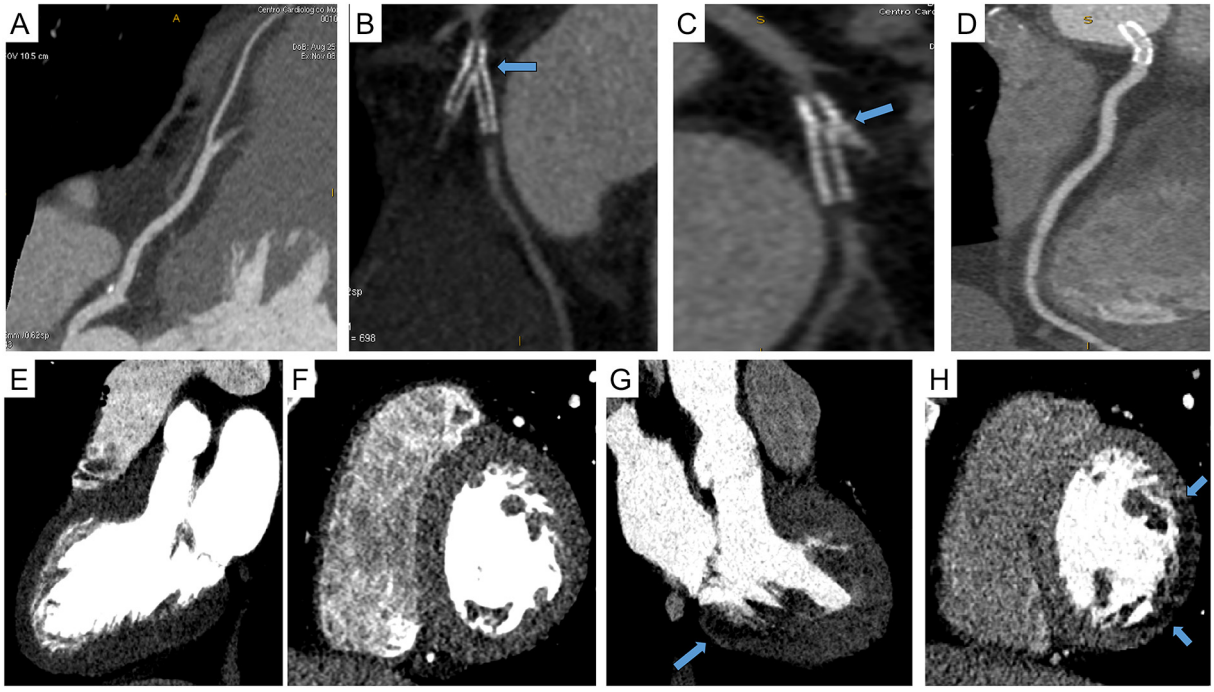

Fig. 2. A patients with previous stent on LCX and RCA underwent stress-rest CTP. LAD (panel A) was free from significative coronary disease and previous stent on ostial RCA was patent (panel D); on the contrary previous a significative intra-stent restenosis was evident on LCX-MO at CCTA (panel B–C). Rest CTP showed no myocardial perfusion deficit (panel E–F), while on stress CTP a transmural hypo-enhanced region appeared on posterolateral wall, suggesting inducible myocardial perfusion deficit (panel G–H).

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guided strategy cost was $8127 vs. $12,145 with a usual care strategy ($p < 0.0001$), not accounting for the cost of the FFR_{CT} test. The mean costs remained 26% lower among the FFR_{CT} patients than among usual care patients ($9036 vs. $12,145, $p < 0.0001$) when factoring in the cost of the FFR_{CT} analysis [16].

In the multicenter ADVANCE Registry, a large prospective examination of using FFR_{CT} diagnostic pathway in real-world settings(5083 patients), no death or MI occurred within 90 days in any subject whose FFR_{CT} was >0.80 [17]. Other real-world reports have also demonstrated the safety of deferral ICA based on the FFR_{CT} result [18]. These observational data should be interpreted in the context of a single arm design of the studies and lack of independent adjudication.

2.2.3. FFR_{CT}: As the preferred non-invasive test

The PACIFIC FFR_{CT} sub-study provided the first head-to-head comparison between CCTA, SPECT and PET for the diagnosis of ischemia using invasive FFR as a reference. FFR_{CT} outperformed CCTA, SPECT and PET in terms of sensitivity, was significantly more accurate than CCTA and SPECT and had higher specificity than SPECT. In an intention to diagnose analysis FFR_{CT} performance was equivalent to SPECT but inferior to PET for diagnosing myocardial ischemia [19]. These data suggest that FFR_{CT} may have advantage over other non-invasive test.

Today, clinical evidence alongside the current widespread availability of CCTA, the low radiation dose associated with the current technology of CT scanners, fast processing times of FFR_{CT} and emerging reimbursement by national health care systems challenge existing diagnostic pathways. The guideline in the United Kingdom has recommended use of CCTA with selective FFR_{CT} as first-line diagnostic test on the basis of cost and diagnostic certainty [20]. Further research will help identify the most cost-effective approach to identify patients with significant CAD.

2.2.4. FFR_{CT} for risk stratification

The evaluation of coronary resistance by FFR_{CT} may enhance risk stratification using hemodynamics metrics. In the EMERALD trial, seventy-two patients with documented ACS and available CCTA acquired between 1 month and 2 years before the development of ACS were analyzed. The culprit lesions showed higher prevalence of adverse plaque characteristics (80.3% vs. 42.0%; $p < 0.001$) than non-culprit lesions. Hemodynamic findings associated with plaque rupture were: low distal FFR_{CT}, higher $\triangle FFR_{CT}$ across the lesion, wall shear stress and axial plaque stress. Therefore, the integration of noninvasive hemodynamic assessments on top of high risk anatomical features may improve the identification of potential culprit lesions for future ACS [21].

2.2.5. FFR_{CT} for treatment decision and follow-up in complex CAD

In patients with multi-vessel disease, physiologic three-vessel assessment provides a complete functional evaluation of the ischemic burden. Nevertheless, despite the benefit observed in randomized trials, routine invasive three vessel interrogation by invasive pressure wire is seldom performed. Using FFR_{CT}, approximately 30% of patients with three-vessel disease can be re-classified to a lower risk category; therefore, modifying their treatment options. The SYNTAX III Revolution trial evaluated the agreement on treatment decision-making between either CCTA or ICA randomizing two heart teams to assess CAD in patients with left main or three-vessel disease. SYNTAX III showed an almost perfect agreement between the clinical decision (surgery or PCI) derived from CCTA and ICA (kappa coefficient 0.82;95%CI 0.74–0.91). The use of FFR_{CT} changed treatment recommendation in 6% and treatment planning in 16% [22]. These results suggest that clinical decision making between CABG and PCI based solely on non-invasive CCTA and FFR_{CT} is feasible. However, an outcomes trial testing this hypothesis is warranted to confirm the feasibility and safety of this approach.

2.2.6. Emerging tools based on FFR_{CT}; Planning your revascularization

CCTA with FFR_{CT} is able assess the anatomical and functional pattern of CAD (i.e. focal or diffuse) [23]. FFR_{CT} can provide an FFR value at any position of the coronary tree allowing for the assessment of the distribution of epicardial resistance non-invasively. Identifying the functional CAD pattern influences therapeutic options. PCI is likely to restore coronary physiology and relieve ischaemia in cases of focal CAD; whereas the clinical benefit of PCI in cases of diffuse CAD can be questioned. Diffuse CAD is readably assessed with CCTA by assessing the distribution of atherosclerotic plaque along the vessel. Similarly, FFR_{CT} can determine whether pressure drops are focal or gradually distributed in the coronary vessel [24,25].

A novel noninvasive FFR_{CT}-based planner tool (HeartFlow Planner) provides luminal remodeling using computer software enabling recalculation of the FFR after virtual removal of coronary artery stenoses and prediction post PCI FFR_{CT}. This technology is based on a geometric modeling technique to enable physicians to efficiently update the luminal geometry and employ a rapid blood flow solver to compute changes in FFR_{CT} in the updated geometry. This stenosis removal process virtually mimics stent implantation providing the virtual equivalent of the invasive FFR value measured after PCI [26]. This is the subject of ongoing validation in the Precise PCI Plan (ClinicalTrials.gov: NCT03782688).

2.3. Critical appraisal

The initial validation studies of the FFR_{CT} technology included patients with intermediate degree of stenosis at CCTA (50–70%) and have shown good accuracy and precision. The uncertainty around the FFR_{CT} value has shown a mean difference of 0.03 and SD of 0.07 with invasive FFR as a reference. This variability with FFR in absolute numbers should be accounted for in the clinical decision-making process. Cases with FFR_{CT} close to the cutoff of 0.80 might require confirmatory invasive FFR evaluation. Nevertheless, the observational data showing very low rate of adverse events in patients deferred from revascularization based on FFR_{CT} is reassuring. Moreover, higher degrees of calcification could influence the accuracy of FFR_{CT} results; however, in clinical studies FFR_{CT} proved to have an incremental value over CCTA alone for the identification of hemodynamic significant calcific CAD. The high accuracy of FFR_{CT} in heavily calcified lesion may be partially explained by the quality assessment process performed prior to the FFR_{CT} computation. Use of machine-learning algorithms may further overcome this issue. The benefit of FFR_{CT} on top of CCTA in severe CAD (stenosis >70%) might also be more limited in comparison with its role in the intermediate stenosis range. None of the trials to date have specifically assessed the diagnostic capabilities of FFR_{CT} in this high degree stenosis CAD.

In a PACIFIC sub-study, 25% of CCTA's was not evaluable by FFR_{CT}. In the recent SYNTAX III Revolution trial, using one specific and last generation CT scanner, FFR_{CT} analysis was feasible in 88% of a complex CAD population. Acceptance rates of CCTA images for FFR_{CT} analysis are prone to staff experience and depend on CT hardware and optimal patient preparation. Randomized trials are still needed to test the clinical benefit of FFR_{CT} on top of CCTA concerning clinical outcomes. Lastly, the cost-effectiveness outcomes of the inclusion of FFR_{CT} across the pathway of patient care require further evaluation.

2.4. Future perspectives

Two future randomized trials will examine the position of FFR_{CT} in the mainstream of stable CAD diagnosis and treatment. The PRECISE trial will evaluate whether an evaluation combining risk stratification using the PROMISE Risk Tool with CCTA and selective FFR_{CT} could improve outcomes over usual care while safely deferring further testing in low-risk patients. The DECISION trial will randomize patients between angiography and FFR- or non-hyperaemic pressure ratio-guided

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revascularization vs. a FFR_{CT}-guided strategy incorporating clinical decision making based on the HeartFlow Planner.

The aforementioned trials will provide data on the clinical benefit of a FFR_{CT} diagnostic strategy. Until now, non-invasive cardiac testing have been unable to identify which patients may benefit from revascularization. CCTA and FFR_{CT}, by providing a vessel level evaluation of epicardial resistance may prove to better identify patients that benefit from PCI or CABG.

3. CT perfusion

3.1. Static CT perfusion

3.1.1. Technical principles

Myocardial perfusion by cardiac computed tomography (CTP) enables evaluation of myocardial perfusion during both rest and stress (hyperemia) conditions, similarly to other noninvasive imaging techniques such as stress cardiac MR and nuclear imaging [27] (Fig. 2). Iodinated contrast attenuates X-rays proportionally to iodine content in tissue; thus, myocardial perfusion defects can be directly visualized as hypo-attenuated or non-enhancing regions. The static CTP imaging is based on acquisition of one single phase during the first-pass of the contrast agent; accordingly, one the major drawback of this technique is that the peak attenuation may be missed because only one sample of data is acquired [27].

There are two protocols mostly used, named according to the sequence of scan acquisitions: rest/stress or stress/rest. An interval of 10–15 min between the two sequences provides optimal contrast wash-out [27]. The rest/stress protocol uses the ability of CCTA to rule out obstructive CAD and the stress CTP is performed only in the presence of anatomically of intermediate CAD. This protocol is limited by the cross-contamination of contrast in the stress phase and beta-blocker administration before the rest acquisition, leading to a possible underestimation of myocardial ischemia. The stress/rest protocol is optimized for the detection of myocardial ischemia if a complete wash-out from anti-ischemic therapy (i.e. beta-blocker) can be obtained. However, performing stress CTP first may mask a fixed perfusion defect secondary to residual contrast media contamination in the rest phase, reducing sensitivity for infarction detection [27].

Visual assessment of CT perfusion images is the most common approach for qualitative assessment of myocardial perfusion. Areas of reduced perfusion appear hypo-enhanced compared with the normal myocardium, which implies either myocardial ischemia or myocardial infarction. Hypoperfusion in stress with normal perfusion in rest underlines ischemia, whereas hypoperfusion in stress that persists with same extension in rest is indicative of necrosis [28]. A narrow window width and level (200 to 350 W and 150–200 L) is recommended for perfusion defect evaluation.

In a static CTP protocol, review of multiple cardiac phase images can help to distinguish true perfusion defects from motion or beam-hardening artifacts [29–30]. In addition, true perfusion defects may persist on stress images throughout all cardiac phases, from systolic to diastolic. Unlike true perfusion defects, motion or beam hardening artifacts do not correspond to a coronary territory and might appear in only 1 or 2 cardiac phases [29].

The transmural perfusion ratio (TPR), defined as the ratio of segment-specific subendocardial attenuation to subepicardial attenuation, has been introduced as a quantitative index of static CTP. However, recent studies demonstrated that visual assessment of static CTP provides superior diagnostic performance over the TPR [29–33].

3.1.2. Overview of the current evidence

The diagnostic accuracy of CTP has been compared with that of other noninvasive imaging modalities, including SPECT, PET and MR [33–35] (Table 2). In a meta-analysis performed by Pelgrim et al. [36], CTP showed good diagnostic performance, with a sensitivity ranging from 75 to 89% and specificity from 78 to 95% compared with ICA, SPECT or MR.

The CORE320 study compared the diagnostic performance of static CTP acquired by a wide-detector scanner in 381 patients with SPECT and ICA [37]. In this study, the integrated CCTA-CTP diagnostic accuracy for detecting or excluding flow-limiting CAD showed an AUC of 0.87 [95% CI:0.84–0.91]. The PERFECTION study [38] evaluated the diagnostic accuracy of CTP, performed with a whole-heart coverage CT scanner by using ICA plus invasive FFR as the reference standard in 100 intermediate-to high-risk patients. CCTA alone demonstrated diagnostic accuracy of 83% and 76% in a per-vessel and per-patient analyses, respectively. Combining CCTA with stress CTP, per-vessel and per-patient accuracy were 93% and 91%, respectively.

The CATH2 was a randomized controlled trial aimed at evaluating the clinical efficacy of combined CCTA-CTP [39] in 300 patients hospitalized for acute-onset chest pain. A post-discharge diagnostic strategy of coronary CTA + CTP safely reduced the need for invasive examination and treatment in patients suspected of having ischemic heart disease.

3.1.3. Main clinical applications

Current evidence suggests that adding CTP imaging is a safe and good tool to improve the accuracy and the positive predictive value of CCTA alone. The combination of these two diagnostic methods provide anatomic information concerning luminal stenosis, plaque morphology, total plaque burden and also provides data on myocardial perfusion. Another setting in which CTP can improve the diagnostic accuracy of CCTA is patients with previous percutaneous interventions with metallic stents, as recently demonstrated by the ADVANTAGE study. Here, 150 patients previously treated with PCI underwent both stress CTP + CCTA and ICA, suggesting that CTP significantly improves the diagnostic accuracy of CCTA alone [40].

3.2. Dynamic CT perfusion

3.2.1. Technical principles

A dynamic CTP acquisition protocol is used to obtain a quantitative evaluation of myocardial perfusion and myocardial blood flow [41]. Patient preparation and pharmacological stress protocol are similar to static CTP; nonetheless, with dynamic CTP acquisitions repeated rapid CT scans during intravenous contrast medium injection are acquired to derive time-attenuation curves (TACs). From TACs a value of myocardial blood flow (MBF) is then obtained through different methods, all based on the dynamic change of attenuation values, that are proportional to concentration of contrast material in the myocardium and of consequence to MBF [42–43]. The post-processing phase is of utmost importance and regions of interest on myocardium, usually identifying 16-segments heart model, need to be correctly positioned.

After adequate post-processing, semi-automatic software provides a quantification of MBF, that is usually expressed as ml/100 ml/min for every segment of myocardium analyzed.

Clinical interpretation follows the common principles of myocardial perfusion physiology, similarly to static CTP.

3.2.2. Analysis of the current literature

In 2008, a first in human study with 16-slice CT scanner compared CTP to myocardial scintigraphy with promising results [44]. Similar findings were reported in 2012 by So et al. with 64-slice scanner at the expense of higher radiation dose (19.4 mSv) [45]. In 2014, Rossi et al. suggested that dynamic CTP had higher diagnostic accuracy than anatomical evaluation of coronary artery by CCTA when compared with invasive FFR, using a second-generation CT-scanner(AUC 0.95 vs. 0.89, respectively) [46].

In 2018, a meta-analysis was performed including 13 studies and 482 patients. Most of the studies used adenosine as hyperemic agent and dual-source CT was the most represented scanner type (69%). Dynamic CTP showed good diagnostic performance compared to different

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Table 2
Static and dynamic CTP previous studies.

Author	Year	N of patients	Clinical setting	Type of CT scanner	CT perfusion protocol	Gold standard	Level of analysis	Sn (95%CI)	Sp (95%CI)	Acc (95%CI)	Dose (mSV)*
Static CTP											
Blankstein et al.	2009	34	Suspected and stable CAD	64-slice dual source	Stress-rest	SPECT MPI	Vascular territory	84 (69–94)ᶜ	78 (56–93)ᶜ	n.p.	12.7 ± 4
Rocha-Filho et al.	2010	35	Suspected and stable CAD	64-slice dual source	Stress-Rest	QCA (stenosis>50%)	Vessel	91 (77.4–97.3)°	91 (80.4–96.4)°	n.p.	11.8 ± 4.5
Ko et al.	2011	50	Only suspected CAD	64-Dual source	Only Stress	MRI	Vessel	91	72	83	8.6 ± 1.6
Feuchtner et al.	2011	30	Suspected and stable CAD	128-slice dual source	Stress-rest	QCA (stenosis>70%)	Vessel	100 (94–100)°	74 (48–89)°	95	2.5 ± 2.1
Ko et al.	2012	40	Only suspected CAD	320-slice	Rest-stress	Invasive FFR	Vessel	87 (72–95)°	95 (87–98)°	92	9.2 ± 3.5
George et al.	2012	50	Suspected and stable CAD	320-slice	Rest-stress	SPECT MPT	Vessel	72 (46–89)ᶜ	91 (74–98)ᶜ	n.p.	13.8 ± 2.9
Bettencourt et al.	2013	101	Only suspected CAD	64-slice	Stress-rest	Invasive FFR	Vessel	71 (62–79)	90 (87–92)	85	5 ± 0.96
Wong et al.	2013	75	Suspected and stable CAD	320-slice	Rest-stress	Invasive FFR	Vessel	88°	83°	84	9.8
Rochitte et al.	2013	381	Suspected and stable CAD	320-slice	Only stress	SPECT MPI	Vessel	78 (73–82)ᶜ	62 (58–67)ᶜ	n.p.	5.3
Yang et al.	2015	75	Only suspected CAD	Dual source	Stress-rest	Invasive FFR	Vessel	86 (75–94)°	85 (57–98)°	87	n.p.
Cury et al.	2015	110	Suspected and stable CAD	Multivendor	Stress-rest	SPECT MPI	Patient	90 (71–100)ᶜ	84 (77–91)ᶜ	n.p.	17.7 ± 6.8
Pontone et al.	2018	147	Only suspected CAD	256-slice	Rest-stress	Invasive FFR	Vessel	92 (87–97)°	95 (92–97)°	94 (91–96)°	5.2
Andreini et al.	2019	100	Known CAD with prior PCI	256-slice	Stress-Rest	QCA (stenosis>50%)	Patient	100 (93.4–100)°	84.0 (63.9–95.5)°	94.9 (87.5–98.6)°	4.15 ± 1.5
Dynamic CTP											
Ho KT et al.	2010	35	Suspected and stable CAD	128-slice dual source	Stress-rest§	SPECT MPI	Segment	83ᶜ	78 ᶜ	n.p.	18.4
Wang et al.	2012	30	Only suspected CAD	128-slice dual source	Rest-stress§	SPECT MPI	Vessel	90°	81.4°	n.p.	12.8 ± 2.6
Huber et al.	2013	32	Only suspected CAD	256-slice dual source	Stress only	Invasive FFR	Patient	75.9 (56.5–89.7)ᶜ	100 (94.6–100)ᶜ	n.p.	9.5
Kim et al.	2013	33	Only suspected CAD	128-slice dual source	Stress-rest§	Stress MRI	Segment	81 (70–92)ᶜ	94 (92–96)ᶜ	93 (91–95)	10.3 ± 1.1
Rossi et al.	2014	80	Only suspected CAD	128-slice dual source	Rest-stress§	Invasive FFR	Vessel	88 (74–95)ᶜ	90 (82–95)ᶜ	n.p.	13.6
Kono et al.	2014	49	Suspected and stable CAD	128-slice dual source	Rest-stress§	Invasive FFR	Segment	89.9ᶜ	47.8ᶜ	68.1	12.9
Ebersberger et al.	2014	37	Only suspected CAD	128-slice dual source	Rest-stress§	SPECT MPI	Patient	86	96	95	9.6 ± 4.1
Bamberg et al.	2014	38	Suspected and stable CAD	128-slice dual source	Rest-stress§	Stress MRI	Segment	69.6 ᶜ	70.5ᶜ	70.3	16.9 ± 3.2
Tanabe Y et al.	2016	39	Only suspected CAD	256-slice dual source	Stress-rest§	Stress MRI	Segment	82 (76–88)ᶜ	87 (80–92)ᶜ	n.p.	n.p.
Coenen A et al.	2017	74	Suspected and stable CAD	128-slice dual source	Rest-stress§	Invasive FFR	Segment	73 (61–86)°	84 (75–93)°	79 (71–87)	13 ± 2.5
Pontone et al.	2019	85	Only suspected CAD	256-slice	Rest-stress§	QCA + iFFR	Vessel	73 (63–83)°	86 (81–91)°	82 (77–87)	8.1 ± 1.1

*Including both rest and stress CTP (complete CTP protocol) ° for integrated CTA + CTP ᶜ for CTP alone; § Rest for CCTA only.
Sn: Sensitivity; Sp: Specificity; Acc: Accuracy; CAD: coronary artery disease; CTP: computed tomography perfusion.

reference standards, including invasive FFR. Sensitivity and specificity of 83% and 90% at the segment level, and of 93% and 82% at the patient level, respectively, were reported. However, mean radiation dose ranged from 5.3 to 10.5 mSv for the dynamic perfusion and from 9.5 to 18.4 mSv for the entire CT scan protocol, including coronary anatomy evaluation (Table 2) [47].

To the best of our knowledge, only few studies addressed the prognostic role of dynamic CTP. In 2017, Meinel FG et al. enrolled 144 patients who underwent both CCTA and dynamic CTP; here CTP had incremental predictive value over clinical risk factors and detection of CAD with CCTA [48]. More recently, CCTA, FFR_{CT} and dynamic CTP were evaluated in a multicenter trial that included 84 patients; authors demonstrated that myocardial blood flow evaluated by dynamic CTP has the highest prognostic value, over CCTA and FFR_{CT}, in terms of future MACE at an 18 months follow-up [49].

3.2.3. Main clinical applications

Dynamic CTP should be performed with new generations of CT scanners to reduce radiation dose. Dynamic CTP with last generation CT scanner can be used for accurate quantification of MBF and results obtained in recent studies demonstrated that dynamic CTP may have a prognostic role over anatomical evaluation and FFR_{CT} [49]. The main advantage over static CTP is the possibility to quantify MBF that is of fundamental importance to diagnose myocardial ischemia, in cases of multivessel disease where extensive but balanced ischemia may be underestimated and to detect microvascular angina. So far different blood flow cut-off values have been reported, ranging from 75 ml/100 g/min to >100 ml/100 g/min.

3.2.4. Future perspective

When coronary atherosclerosis is identified by CCTA, different pathways may be taken depending on the specific angiographic findings,

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patient risk profile, and individual preference. These paths may include direct referral for ICA, optimal medical therapy or additional noninvasive ischemia testing to evaluate the functional significance of the findings. Prognostic studies are needed to assess if a combined approach (CCTA+CTP) will have substantial impact on treatment costs, patient management, and outcome. The time to challenge this hypothesis with randomized prospective trials has come.

3.2.5. Critical appraisal

Radiation dose is one of the main concerns regarding CTP use in the clinical routine; in the most of studies available, it remains between 5 mSv and 10 mSv for static CTP and beyond 10 mSv for dynamic CTP. This would be of particular concern in patients with diffuse and progressive coronary atherosclerosis in whom serial scan evaluations would be needed to determine appropriateness and timing of myocardial revascularization. Of note, taking into consideration the elevated sensitivity but limited specificity of CCTA for the detection of significative coronary stenosis, patients with moderate and diffuse coronary lesions or patients already revascularized may particularly benefit from CTP on top of CCTA. A recent study performed in stented patients reports higher CCTA+CTP diagnostic accuracy vs. ICA when compared to CCTA alone, at the expense of low radiation dose (4.15 ± 1.5 mSv) [40]. However, it must be underlined that these results were obtained with a last generation CT scanner that is still not widely available.

A second potential limitation to the wide diffusion of stress CTP in the clinical setting is that both cardiological and radiological competences must be available in order to perform a safe and high-quality exam.

4. Conclusions

The most appropriate and comprehensive diagnostic flow-chart for patients with stable CAD is an evolving and still unresolved matter of debate. CCTA may provide an accurate and integrated evaluation of patients with suspected CAD offering both anatomical and functional assessment in one single technique. More specifically, adding stress CTP/FFR_{CT} on top of CCTA alone may help physician to better identify patient who may merit PCI or CABG, reducing the possible "over-indication" to myocardial revascularization after CCTA that has been previously described [1–2].

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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