



How to perform and evaluate a myocardial perfusion imaging by computed tomography

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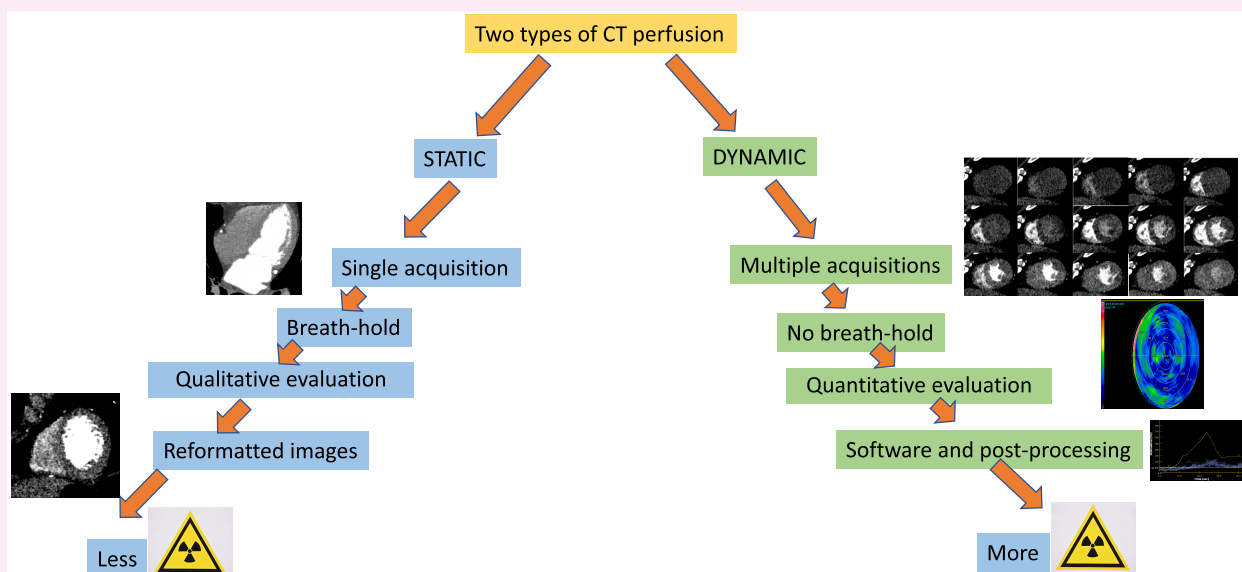
Stress computed tomography perfusion (CTP) delivers a comprehensive evaluation of both the anatomical and functional aspects in a single examination. It stands out as the only non-invasive technique capable of quantifying coronary stenosis and assessing its functional impact, offering a consolidated diagnostic and management approach for patients with confirmed or suspected coronary artery disease (CAD). This very practical review ('How to..' approach) provides guidance on conducting and interpreting static and dynamic CTP, along with an analysis of the strengths and limitations of these methodologies.

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Graphical Abstract



Keywords

coronary artery disease • myocardial perfusion • computed tomography

Introduction

The most appropriate and comprehensive diagnostic flow chart for patients with stable coronary artery disease (CAD) is an evolving and still unresolved matter of debate. Anatomical imaging of the coronary arteries using computed tomography angiography (CCTA) has a very high negative predictive value in patients with low-to-intermediate risk of its diagnostic and prognostic role to rule out CAD with low radiation exposure, and these are the main reasons for its recommendation as an early test to rule out disease.^{1–4} In contrast, cases of patients with known or previously revascularized CAD are significantly more complex, challenging the role of non-invasive coronary artery imaging. In these patients, the addition of functional information is prognostically useful⁵ and in patients with previous history of percutaneous coronary intervention (PCI), functional strategy has been shown to be more cost-effective as compared to anatomical assessment.⁶

CT myocardial perfusion imaging (CTP) has been demonstrated as a technique offering a unique and comprehensive tool for the evaluation of patients with stable chest pain, providing information on coronary atherosclerosis and myocardial perfusion during the same session.^{7,8} CTP has been validated against a clinically well-accepted approach [combined invasive coronary angiography (ICA) and single-photon emission computed tomography (SPECT)],⁹ SPECT,¹⁰ stress cardiac magnetic resonance,¹¹ and invasive fractional flow reserve (FFR).¹²

Imaging of myocardial perfusion with CT was performed as early as the 1980s, but its routine clinical use has remained limited, due to technical issues that could not be addressed with earlier CT technology.^{13–15}

The technical improvements of CT scanners, such as increased temporal and spatial resolution and increased coverage, have renewed in the latest years the interest in performing myocardial perfusion CT imaging.^{16–18}

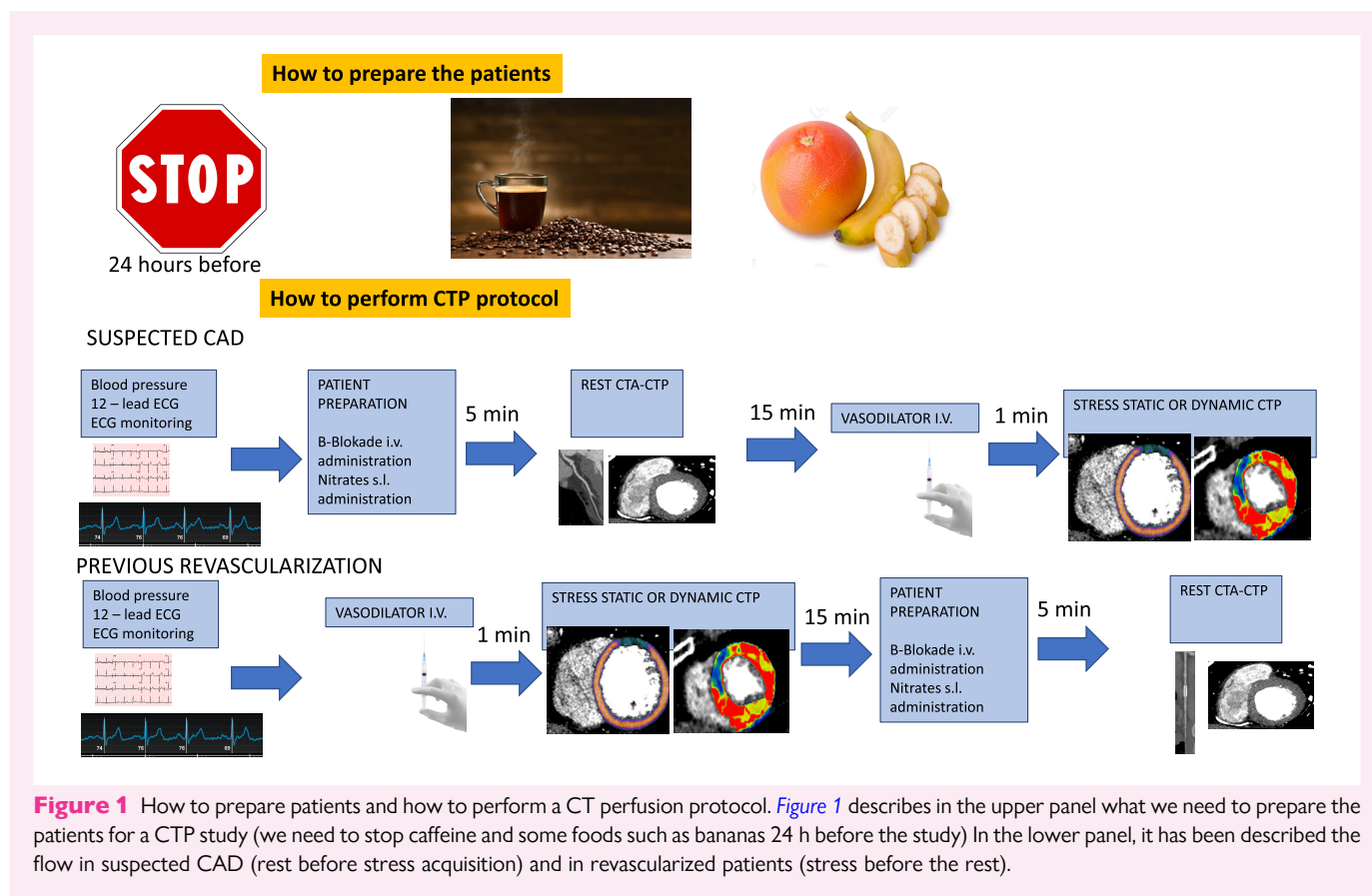
There are two main methods for CTP acquisition: static and dynamic myocardial CTP that will be discussed in this practical review ('How to..' approach).

How to prepare patients

ECG monitoring and measurements of blood pressure are performed. Two intravenous (IV) lines are essential for CTP studies: one for contrast injection and another for the administration of the vasodilator agent (adenosine or dipyridamole). If regadenoson is used, then we need only one venous access. Patients are asked to observe a fast for 6 h before the scan and to refrain from taking caffeine for 24 h prior to the scan. Caffeine is a competitive inhibitor of the adenosine receptor, and thus, its ingestion can lead to suboptimal pharmacological stress and a false negative scan. Prior to rest CTCA, rate-limiting medication such as beta-blockers may be required to optimize the heart rate and sublingual glyceryl tri-nitrate can be administered to improve visualization of the coronary arteries. *Figure 1* describes how to prepare patients (upper panel). *Table 1* describes the main differences among the vasodilators in terms of mechanism of action, half-life, and way of infusion.

Contrast media injection protocol

For both rest and stress CT scans, an intravenous low-iodine contrast agent has to be administered using a power injector. The contrast volume is related to the patient's weight and the type of scanner used, ranging from 60 to 120 mL in single-energy CT scanners. It can be significantly reduced if dual-energy CT (DECT) technique is applied or if a wide-coverage CT scanner is used (50 mL). The contrast bolus should be delivered with a total injection time of 10 s or less. It is recommended to inject a saline chaser (40–50 mL) following the iodine contrast bolus. CT perfusion techniques are used to image the transit of contrast material from the coronary arteries to the myocardium. Because iodinated contrast material attenuates X-rays proportional to the concentration of iodine, hypoattenuated areas in the myocardium represent myocardial regions of hypoperfusion and/or reduced intravascular blood volume.



How to perform CT myocardial perfusion

In *Figure 1* (lowers two panels), the workflow of the CTP protocol is described in a subset of patients with suspected CAD and previous revascularization.

Two CT scans have to be carried out: one with pharmacological stress and another in rest condition. A third, optional, delayed CT acquisition can be performed to complete the CT perfusion protocol for the discrimination between viable and nonviable myocardium. The decision to select the opening scan (rest or stress) depends on the pre-test probability of CAD, previous revascularization, and/or the extent of calcium score. It is better to start with the stress phase among patients with intermediate-to-high pre-test and with moderate-to-high calcium scores, and in patients with previous revascularization, as ischaemia needs to be prioritized. When stress CT imaging is performed first, the myocardium is not contaminated by any previous contrast media and so the detection of ischaemia is optimized. On the other hand, it is preferred to initiate the rest phase if the patient has a low to intermediate probability of CAD with no calcium or mild calcium in the coronary arteries, as it is highly probable that the patient has normal coronary arteries, and the high negative predictive value of the CCTA will allow to rule out CAD and thus won't require to continue with the stress phase.

Static CTP

How to acquire static CTP

Static myocardial CTP, which has been more extensively investigated, refers to the assessment of myocardial perfusion obtained from a single

data sample of contrast enhancement acquired during the first-pass enhancement of CTCA.¹⁹ Static CT perfusion imaging is highly dependent on the contrast material bolus timing.

How to evaluate static CTP

Visual assessment of CT perfusion images is the most common approach for qualitative assessment of myocardial perfusion. The normal myocardium enhances homogeneously after the injection of intravenous contrast material. During the first pass, contrast material diffuses to the interstitial space with a homogeneous incremental increase of myocardial signal intensity over time, which is directly proportional to the iodine content in the tissue. Normal left ventricular myocardial enhancement demonstrates substantially lower attenuation in the lateral wall when compared with the anterior, septal, and inferior walls in patients with normal coronary arteries. The lateral myocardial wall is located adjacent to the air within the lungs and is not subjected to the same beam-hardening effect as the inferior and the septal myocardium, which is located near more dense thoracic structures. This may result in a lower attenuation.²⁰ The myocardium will be evaluated on short-axis (apical, medium, and basal slices) and long-axis views (two-, three- and four-chamber projections) with 4- and 8-mm-thick average multiplanar reformatted images. A narrow window width and level (200–350W and 150–200 L) is recommended for perfusion defect evaluation. Each myocardial segment will be correlated to the specific coronary territory as described by Cerci *et al.*²¹ Myocardial analysis consists of the evaluation of the myocardium in short-axis views from the apex to the base of the left ventricle, using the 17 segments suggested by the American Heart Association classification.

Static CTP can be semiquantitatively analysed using myocardial CT attenuation in each myocardial segment or subendocardial or epicardial layer.²² The transmural perfusion ratio (TPR), defined as the ratio of

Table 1 Stress agents used for the evaluation of myocardial perfusion

Stress agent	Intravenous access	Mechanism of action	Method and timing of infusion	Half-life	Side effects	Cost
Adenosine	Double access	Coronary vasodilatation induced by not-selective A1 adenosine-receptor stimulation (increasing cellular cAMP levels)	Continuous infusion at a dose of 0.14 mg/kg per minute over 3–5 min	10 s	Facial flushing, diaphoresis, nausea, asthma, bradyarrhythmias	High
Dipyridamole	Double access	Coronary vasodilatation induced by increasing cellular cAMP levels by inhibition of the phosphodiesterase enzymes that normally break down cAMP	Continuous infusion at a dose of 0.56 mg/kg over 4–6 min	25–30 min (need the antidote aminophylline)	Facial flushing, diaphoresis, nausea, asthma, bradyarrhythmias	Low
Regadenoson	Single access	Coronary vasodilatation induced by selective A2A adenosine-receptor stimulation	Intravenously bolus infused in 10 s followed by a saline chaser	2–3 min	Not contraindicated in asthma; headache, dizziness, nausea, stomach discomfort, decreased sense of taste, mild chest discomfort, or warmth, redness, or tingling feeling under your skin	Intermediate-high Not widely available

segment-specific subendocardial attenuation to subepicardial attenuation, has been introduced as a quantitative index of static CTP.²³ However, more recent studies demonstrated that visual assessment of static CTP provides superior diagnostic performance over the TPR.^{22,24}

Strengths and limits of static CTP

Static CT perfusion imaging that is based on a single acquisition after injection of the stress agent is highly dependent on the contrast material bolus timing. A drawback of static CT perfusion is that the peak attenuation may be missed because only one sample of data is acquired.

Another challenge of myocardial CTP is represented by beam-hardening artefacts which could be misinterpreted as perfusion defects.²⁵ With the development of dual-energy CT, beam-hardening artefacts can be attenuated or even cancelled by the generation of monochromatic images at medium-to-high energy levels. Static CT perfusion imaging has been performed by using the dual-energy mode.²⁶ In a static CTP protocol, a review of multiple cardiac phase images can help to distinguish true perfusion defects from motion or beam-hardening artefacts.^{11,22} True perfusion defects are distributed among the coronary territories, from the subendocardial to the transmural myocardial wall.²⁷ 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 artefacts do not correspond to a coronary territory and might appear in only one or two cardiac phases.²⁷ A common location of beam-hardening artefacts is the basal inferior wall, likely due to the nearby enhancing descending aorta and vertebral bodies.

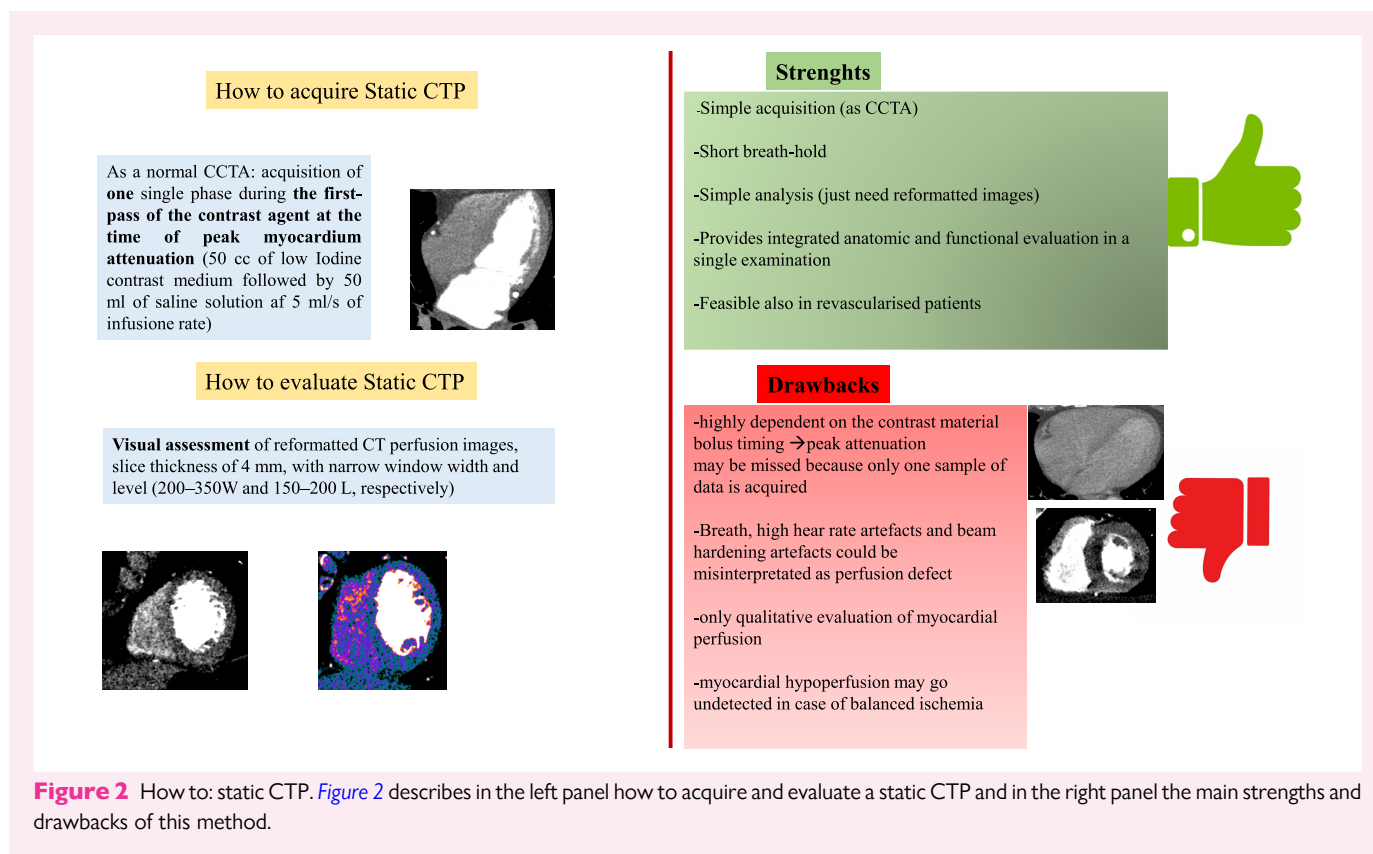
Static CTP may underestimate myocardial hypoperfusion in case of balanced ischaemia (i.e. multivessel coronary artery disease) as it enables only qualitative, or at most semi-quantitative evaluation of myocardial perfusion.²⁸

Figure 2 shows how to acquire and evaluate static CTP and the main strengths and limits of this perfusion approach.

Analysis of the current literature for static CTP

The diagnostic accuracy of CTP has been compared with that of other non-invasive imaging modalities, including SPECT, MRI, and positron emission tomography (PET).^{10,29,30} CTP provides incremental benefit for the diagnosis of haemodynamically significant stenosis defined by FFR, particularly by improving specificity.^{22,30} In a meta-analysis, CTP showed comparable diagnostic accuracy to MRI and PET and was better than SPECT for the detection of myocardial ischaemia defined by FFR.⁸ In a meta-analysis performed by Pelgrim *et al.*, CTP showed acceptable diagnostic performance, with a sensitivity ranging from 75% to 89% and specificity from 78% to 95% compared with invasive angiography, SPECT, or MRI.³¹

The CORE320 study, which is the largest study of CTP thus far performed, compared the diagnostic performance of static CTP acquired by a wide-detector scanner in 381 patients with that of combined SPECT and invasive coronary angiography.⁹ In that study, the combination of CCTA and CTP correctly identified patients with flow-limiting coronary stenosis. In a substudy of CORE320, CTP showed higher diagnostic accuracy than SPECT in predicting obstructive CAD on quantitative invasive coronary angiography.¹⁰ Recently, the PERFECTION study evaluated the diagnostic accuracy of CTP, performed with a whole-heart coverage CT scanner for the detection of functionally significant CAD by using ICA plus invasive FFR as the reference standard in 100 consecutive intermediate- to high-risk symptomatic patients. Authors concluded that the inclusion of stress CTP for the evaluation of patients with an intermediate to high risk of CAD improved the diagnostic performance of CCTA for detecting functionally significant CAD.¹² CCTA alone demonstrated a per-vessel and per-patient



specificity, positive predictive value, and accuracy of 76%, 63%, and 98%, and 54%, 68%, and 76%, respectively. Combining CCTA with static stress CTP, per-vessel, and per-patient specificity, positive predictive value, and accuracy significantly improve in both models (94%, 86%, 93% and 83%, 86%, 91%).

The CATH2 was a randomized controlled trial aimed to evaluate the clinical efficacy of combined examination with CCTA and CTP compared to CCTA alone in 300 patients hospitalized for acute-onset chest pain.³² Patients were randomized 1:1 to examination with coronary CTA or coronary CTA + CTP. The primary endpoint was the frequency of coronary revascularization among patients referred for ICA based on index computed tomography evaluation. A post-discharge diagnostic strategy of coronary CTA + CTP safely reduces the need for invasive examination and treatment in patients suspected of having ischaemic heart disease. Static CTP may also improve CCTA diagnostic accuracy in patients who underwent prior percutaneous intervention with coronary stenting. Rief *et al.* showed that a combined CCTA + CTP protocol improved cardiac CT diagnostic rate and accuracy compared with CCTA alone (100% vs. 78% and 87% vs. 71% at the patient level and vessel level, respectively) in 20 patients previously treated with coronary stenting.³³ Similarly, Magalhaes *et al.* reported a diagnostic accuracy in the territory-based analysis of 91% for CCTA + CTP evaluation vs. 77% for CCTA alone in 46 patients.³⁴ The ADVANTAGE prospective study evaluated 150 patients with previous coronary stent implantation and demonstrated a diagnostic accuracy of CTP significantly higher than that of CCTA in the territory-based and patient-based analysis (92.1% vs. 85.6% and 86.7% vs. 76.7%, respectively) when quantitative coronary angiography was used as a gold standard. Similarly, CTP specificity and diagnostic accuracy were significantly higher than those of CCTA when invasive FFR was employed as a gold standard. Of note, the radiation exposure of cardiac CT (CCTA + CTP) was 4.15 ± 1.5 mSv.³⁵

Dynamic CTP

How to acquire dynamic CTP

Patients preparation, pharmacological stress protocol, and contrast administration do not differ from static CT perfusion; on the contrary, while for static CTP, only one scan is performed at the time of peak myocardium contrast attenuation, for dynamic CTP, during intravenous contrast medium injection, repeated rapid CT scans are acquired to allow determination of time–attenuation curves (TACs). Indeed, dynamic CTP refers to the assessment of myocardial perfusion based on multiple samples of myocardial attenuation at sequential time points of contrast enhancement after injection of a short contrast material bolus to create time–attenuation curves allowing us to quantify myocardial blood flow (MBF). More specifically approximately 20–25 CT scans are performed during contrast medium wash-in and wash-out through the myocardium while patients breath normally; thus, respiratory motion correction is needed in order to reduce motion artefacts. From TACs, a value of myocardial flow is then obtained through different methods; all techniques are based on the dynamic change of attenuation values recorded on the specific regions of interest, which are proportional to the concentration of contrast material in the myocardium and of consequence to myocardial blood flow, even if the relationship between contrast medium retention and myocardial perfusion is not linear and mathematical modelling are needed.^{36–38}

How to evaluate dynamic CTP

After injection of a stress agent repeated rapid CT scans need to be acquired during intravenous contrast medium injection to allow determination of time–attenuation curves (TACs). From TACs, a value of MBF is then obtained through different methods, all based on the dynamic change of attenuation values, that are proportional to the

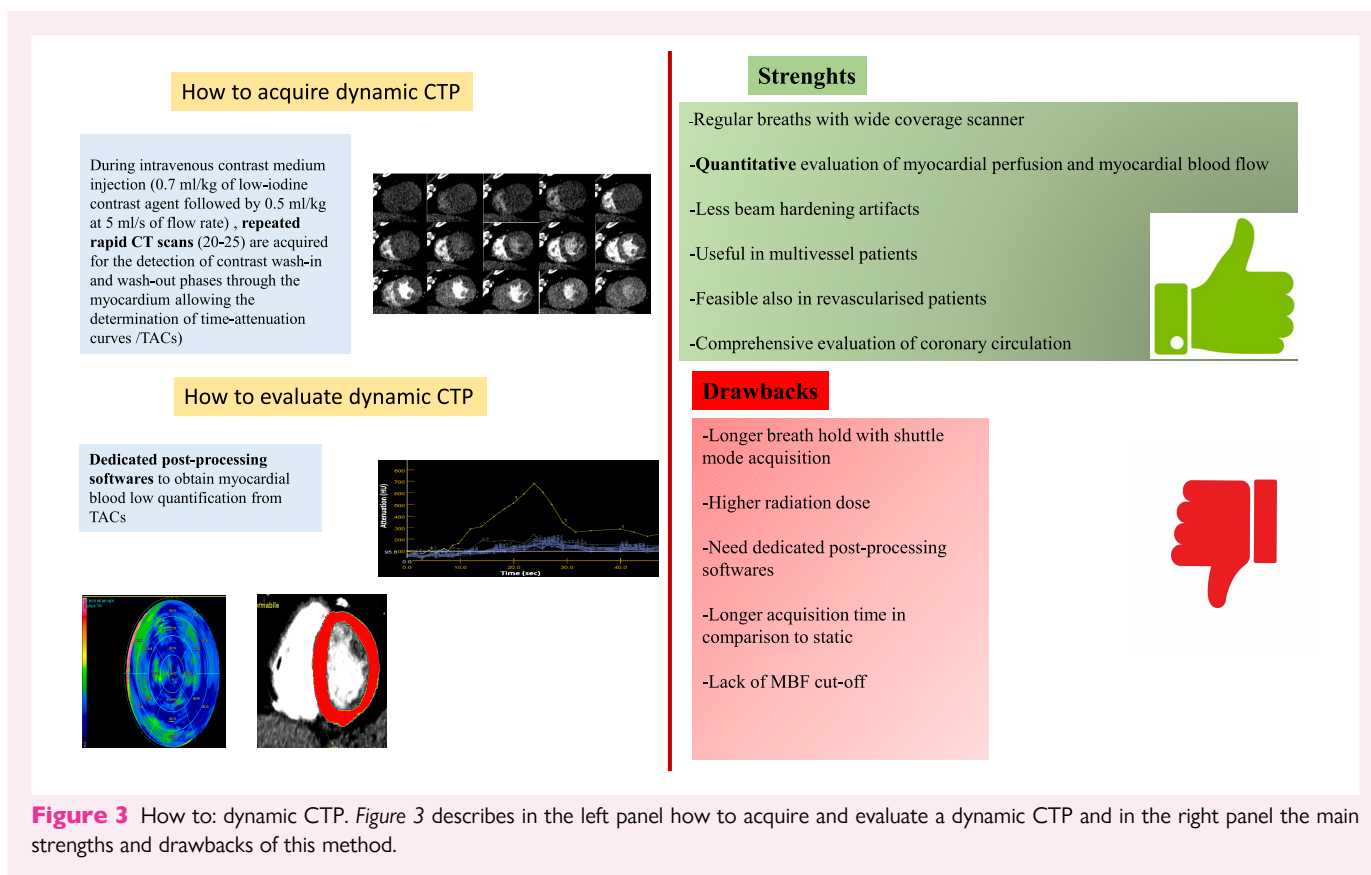


Figure 3 How to: dynamic CTP. *Figure 3* describes in the left panel how to acquire and evaluate a dynamic CTP and in the right panel the main strengths and drawbacks of this method.

concentration of contrast material in the myocardium and of consequence to MBF.³⁶⁻³⁸ In particular, orientation of three- and two-chamber views and short-axis view are obtained. A region of interest in the ascending aorta is placed for arterial input function (AIF) calculation. References of basal anterior and inferior wall and apex are placed for myocardial segmentation in a standard 17-segment model, with endocardial and epicardial borders. For quantification of MBF, myocardial time/attenuation curves are coupled with the AIF using a hybrid deconvolution model. MBF maps were reconstructed as a stack of colour-coded images with a slice thickness of 3.0 mm. Measurements of MBF are automatically calculated as a mean value usually expressed as mL/100 mL/min in every single myocardial segment; point-by-point value is also available. The value of hyperaemic MBF of 101 mL/100 g/min was used as an optimal threshold for absolute MBF to identify functionally significant CAD, as previously validated.³⁹ Nevertheless, substantial divergences in the reported optimal cut-off values and diagnostic accuracy for MBF calculated from CTP datasets have been reported.⁴⁰⁻⁴³ This may be caused not only by technical or methodologic reasons but also by systematic interindividual differences in MBF. As recently reported, a relative measure of focal MBF in comparison with healthy remote myocardium (MBF ratio) may be more accurate for the identification of haemodynamically significant coronary artery stenosis.⁴⁴ A multicentre study indicated that the assessment of MBF ratio allows superior discrimination of significant coronary artery stenosis compared with absolute MBF in patients undergoing coronary CTA and CTP.⁴⁵

Analysis of the MBF ratio may help overcome diagnostic limitations due to methodologic differences or interindividual MBF variability and

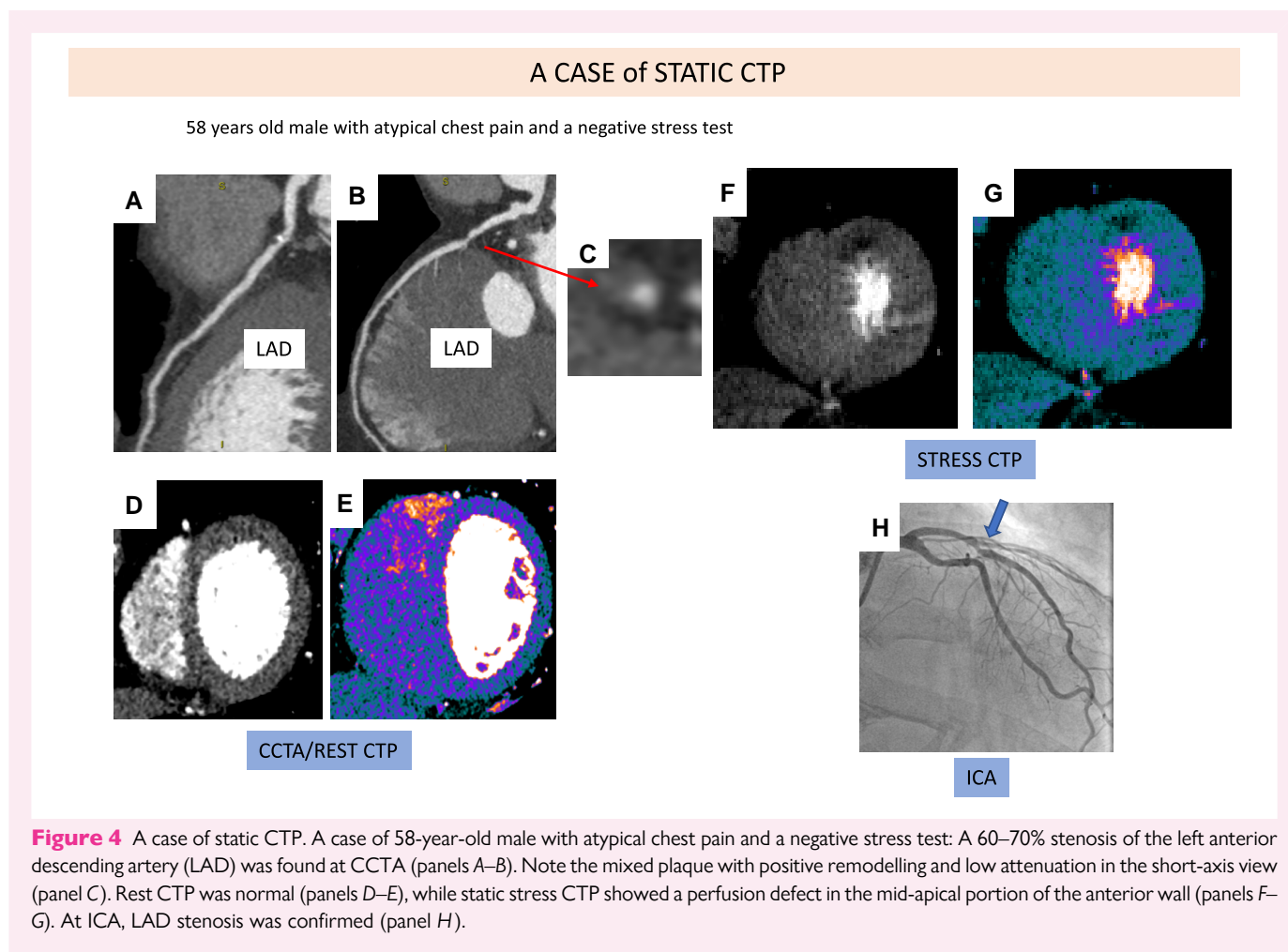
may allow a more robust identification of patients with myocardial ischaemia. *Figure 3* showed how to acquire and evaluate dynamic CTP and the main strength and limits of this perfusion approach.

Strengths and limits of dynamic CTP

One of the major strengths of dynamic CTP is that it is not a subjective and qualitative evaluation of myocardial perfusion but is a quantitative evaluation of perfusion with the calculation of MBF. It does not require breath-hold but regular breaths with a wide-coverage scanner. In comparison with static CTP less beam-hardening artefacts are described although some artefacts (i.e. the presence of very dense structures may cause beam hardening) may result in hypodense areas in myocardium, most commonly on the posterolateral wall, mimicking perfusion defects.³⁸

The dynamic approach has a significant advantage over the static modality, which is represented by the fact that it provides a quantitative measurement of the regional MBF compared to a qualitative assessment of myocardial perfusion only. This is particularly useful in the setting of diffuse CAD, where qualitative perfusion assessment is not sensitive enough and may not be sufficient to identify a functionally significant stenosis in the presence of diffuse and balanced ischaemia.⁴⁶ Despite growing evidence for the diagnostic accuracy of CTP, a robust cut-off value for hyperaemic MBF that allows the identification of hemodynamically relevant stenosis is lacking.

One of the main drawbacks of dynamic CTP is the high radiation dose, which is directly correlated with acquisition protocol; more specifically radiation doses of at least 11 mSv and up to 18 mSv have been previously reported, with further increase if coronary anatomy needs



to be evaluated as dynamic CTP data set cannot be used for coronary anatomy evaluation and a separate CT scan has to be acquired.^{12,43,47,48} With wide-coverage scanners, the radiation dose was lower (5.63 ± 4.2 mSv for the whole cardiac CT exam, CCTA and CTP).³⁹

Analysis of the current literature of dynamic CTP

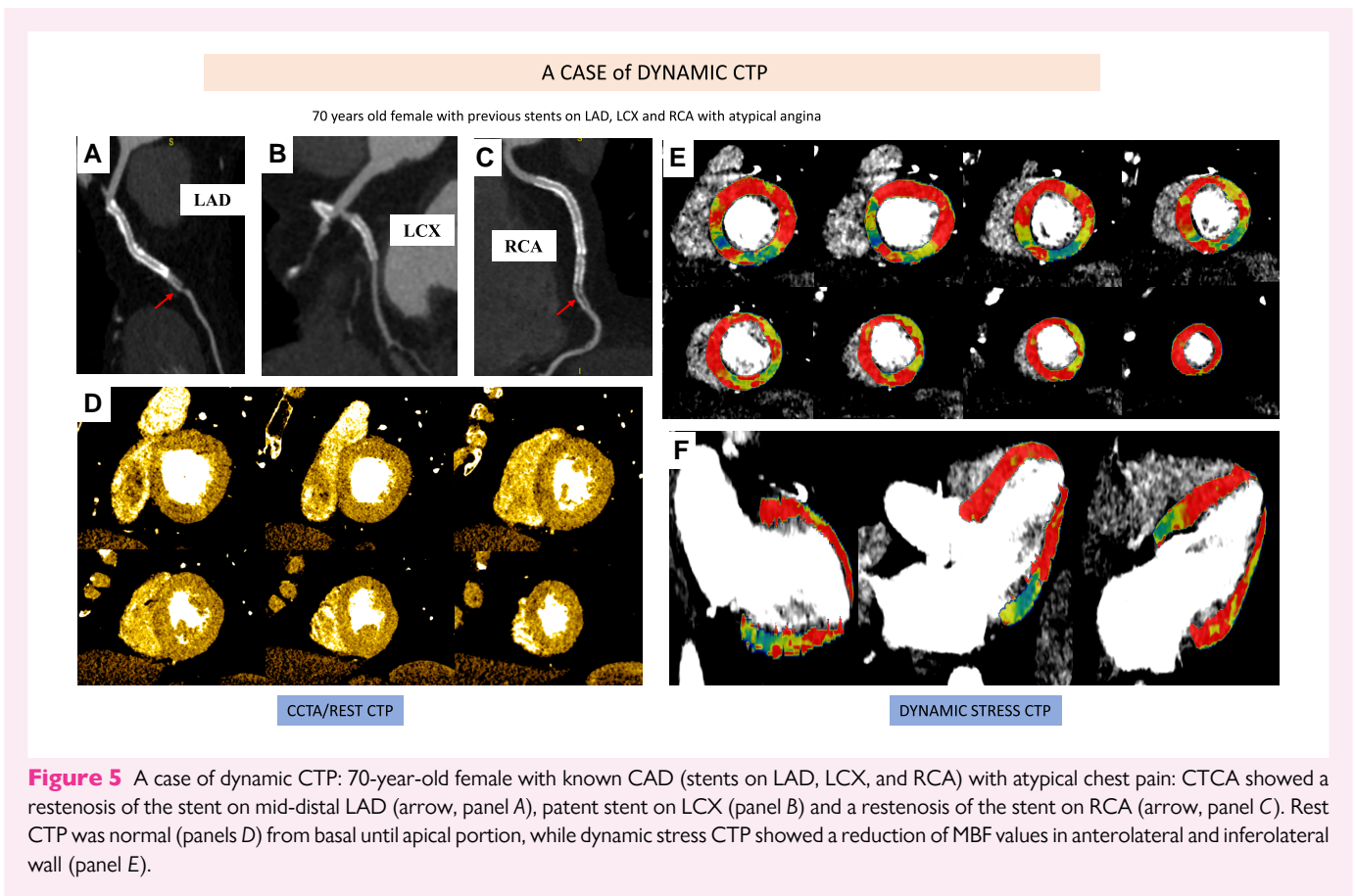
Dynamic CTP for MBF quantification was first described in an animal model in 1987.¹⁵ In 2008, the first human study with 16-slice MDCT compared to myocardial scintigraphy showed promising results; however, it must be underlined that using 16-slice MDCT authors were not able to cover and obtain data from the whole heart.⁴⁹ Similar results were reported in 2012 by So *et al.* with 64-slice MDCT at the expense of high radiation dose (19.4 mSv).⁴⁸ In 2013, Rossi *et al.* suggested that dynamic CTP had high diagnostic accuracy than anatomical evaluation of coronary artery by CCTA when compared with invasive FFR (cut-off of <0.75) using a second-generation CT scanner (AUC, 0.95 vs. 0.89, respectively).⁴³

In 2018, a meta-analysis was performed including 13 studies and 482 patients. Most of the studies used adenosine as a stressor agent, and dual-source CT was the most represented scanner type (69%). Authors reported good diagnostic accuracy of dynamic CTP when compared to different reference standard, including invasive FFR for myocardial ischaemia detection; more specifically, sensitivity and specificity of

0.83 and 0.90 at the segment level, and of 0.93 and 0.82 at the patient level, respectively, were reported. However, radiation dose ranged from 5.3 to 10.5 mSv per dynamic perfusion and 9.3 to 18.1 for the entire CT scan protocol, including coronary anatomy evaluation.⁴⁷

To the best of our knowledge, only a 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; the authors reported that myocardial perfusion CT has incremental predictive value over clinical risk factors and detection of coronary artery stenosis with CCTA.⁵⁰ More recently, CCTA, FFR_{ct}, and dynamic CTP were evaluated in a multicentre trial that included 84 patients; authors demonstrated that myocardial blood flow evaluated by dynamic CTP acquisitions has the highest prognostic value, over CCTA and CT-FFR values, in terms of future major adverse cardiac events (cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, or revascularization) at a mean follow-up of 18 months.⁵¹

Dynamic CTP with last-generation CT scanner may be used for accurate quantification of myocardium blood flow (MBF) and results obtained in recent studies demonstrated that dynamic CTP may have a prognostic role over anatomical evaluation and FFR_{ct}.³⁹ Also, another multicentre trial (SPECIFIC), using third-generation dual-source CT, investigated the diagnostic performance of dynamic stress CTP in addition to CCTA compared to ICA and FFR and demonstrated that Dynamic CTP offers incremental diagnostic value over CCTA alone for the identification of hemodynamically significant CAD.⁵²



Dynamic CTP offers an approach to evaluate the entire cascade of the myocardial perfusion, which translates into a true functional test. This could be particularly important in women and diabetic patients in whom microcirculatory disease could contribute to chest pain. The mean radiation dose ranged from 5.3 for CCTA/static CTP approach to 10.5 mSv for the dynamic perfusion^{35,39}.

Figures 4 and 5 show two cases of static CTP and dynamic CTP, respectively.

Challenging patients (high calcium burden, atrial fibrillation, pacemaker electrodes, and multiple premature beats)

The recent improvements in CT technology with whole coverage detector and increased rotation speed allows to scan also patients in atrial fibrillation and with premature beats in one cardiac beat.¹⁷ Patients with high calcium burden are considered as high pre-test probability of CAD and usually the stress phase is performed before the rest using a Kvp of 100 and 120. Patients with pacemaker are studied as other patients with same anatomical and clinical characteristics but the presence of electrodes can generate some artefacts especially in the septum and inferior wall of left ventricle.

Low kilovolt scanning, new CT detector technology, as photon counting CT and algorithmic solutions are promising approaches to reducing CT radiation dose and image artefacts, also in paediatric patients^{53,54}

Conclusions

Multicenter and multivendor cost-effectiveness studies are required in order to fix clinical indication for obtaining dynamic myocardial CTP imaging and CTP-PRO trial is the first ongoing randomized trial testing the cost-effectiveness of CCTA + CTP with a detailed analysis of the costs of perfusion imaging⁵⁵ CTP would likely find an ideal role in patients with moderate, diffuse multivessel coronary lesions or patients already revascularized, helping physicians to better triage patients, and reducing the possible over-referral to myocardial revascularization after CCTA.^{48,49}

Current evidence suggests that adding static or dynamic CTP imaging is a safe and powerful tool to improve the accuracy and the positive predictive value of CCTA alone because it not only provides anatomic information concerning luminal stenosis, plaque morphology, and total plaque burden but also provides data on myocardial tissue haemodynamics. The combined use of CTA + CTP should be the routine

approach for patients with intermediate stenosis in the setting of suspected CAD and in stented patients.

Lead author biography



Saima Mushtaq is a physician, with a postgraduate in Cardiology in the University of Milan who has dedicated her clinical and scientific activity to Cardiovascular Imaging. Nowadays, she is the Director of Cardiovascular CT under the Post-operative and Cardiovascular Imaging Department of Prof Gianluca Pontone, at Centro Cardiologico Monzino, IRCCS, Milan; she has been councillor of EACVI and vice-chairman of the Italian Group of Cardiac CT. She has more than 200 articles published in peer-reviewed International Journals with Impact Factor regarding Cardiac CT and MRI. She had been part of several multicentre trials. She has the European Certification of MRI (level III) and SCCT Certification for Cardiac CT (Level III).

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Conflict of interest: none declared.

Data availability

No new data were generated or analysed in support of this research.

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