Evaluation of Myocardial Ischemia by Multiple Detector Computed Tomography

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Abstract

For years, cardiovascular diseases have been the leading cause of death worldwide, bringing on important social and economic consequences. Given this scenario, the search for a method capable of diagnosing coronary artery diseases in an early and accurate way is increasingly higher. The coronary computed tomography angiogram is already widely established for the stratification of coronary artery diseases, and, more recently, the computed tomography myocardial perfusion imaging has been providing relevant information by correlating ischemias and the coronary anatomy. The objective of this review is to describe the evaluation of myocardial ischemia by multiple detector computed tomography. This study will resort to controlled clinical trials that show the possibility of a single method to identify the atherosclerotic load, presence of coronary artery luminal narrowing and possible myocardial ischemia, by means of a fast, practical and reliable method validated by a multicenter study.

Introduction

Cardiovascular diseases are the leading cause of death worldwide, bringing on important social and economic consequences. Data from the World Health Organization (WHO) points out that, in 2012, 17.5 mn people died of Cardiovascular Diseases (CVD) all over the world, 7.4 mn of ischemic heart diseases, and 6.7 mn of cerebrovascular accidents. Also according to WHO, heart ischemic diseases are the main death cause in countries with high income and low average income, while, in high average income countries, Cerebrovascular Accidents (CVA) are the main death cause, followed by CVD. In turn, in low income countries, respiratory diseases rank first, followed by HIV/Aids, while CVD is in the fifth place in the list[1].

Currently, we have several noninvasive methods to evaluate myocardial perfusion, such as the color Doppler echocardiography (ECHO), myocardial perfusion scintigraphy (SPECT), Cardiac Magnetic Resonance Imaging (MRI), and, more recently, the Computed Tomography Myocardial Perfusion Imaging (CTP).

The use of these methods allows the noninvasive stratification of Coronary Artery Diseases (CAD) and their functional diagnosis, while the anatomic association and computed tomography perfusion allow a proper therapeutic plan specific for each group of patients.

The Coronary Computed Tomography Angiogram (CTA) allows detecting significant coronary artery disease with high sensitivity and specificity [2-9], and the main recommendation is to eliminate major luminal narrowing in patients with intermediate likelihood of CAD[10]. However, the ability to identify the coronary lesions that cause ischemia is limited[11-13]; although identification is of utmost importance, as the myocardial revascularization is associated with the reduction of mortality and reduction of major cardiac events when the coronary artery luminal narrowing is associated with myocardial ischemia[14-18].

As published in 2007, in the COURAGE study (*Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation Trial*), the percutaneous coronary intervention did not lead to reduction of mortality or nonfatal myocardial infarction compared to the optimized drug therapy if the decision-making was based on the lesion severity[19].

Given this scenario, CTP will be ever more present in the clinical practice. Considering the need to always provide the best care for patients, the search for a method capable of evaluating both anatomy and myocardial ischemia is of great interest. Currently, several prospective studies underway, along with those already published, reveal that this evaluation is possible with multiple detector computed tomography.

With this review, we sought to underline the importance of computed tomography myocardial perfusion imaging due to its potential to evaluate, in a single test, both the coronary anatomy and the myocardial perfusion, adding information which is capital for investigating CAD and defining the therapeutic strategy.

Diagnosis of Myocardial Ischemia

The early diagnosis by clinical evaluation of the risk factors associated with noninvasive diagnostic methods is capital for the CAD management. This association helps arranging reliable information regarding the anatomical and functional diagnosis of obstructive coronary disease, along with appropriate clinical and therapeutic planning.

Both the coronary computed tomography angiogram and the invasive coronary angiography (ICA) provide anatomical data of the coronary arteries, although they cannot help

Keywords

Myocardial Ischemia; Coronary Artery Disease; Multiple Detector Computed Tomography.

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detecting if the coronary artery luminal narrowing leads to hemodynamic repercussion. Currently, the evaluation of myocardial ischemia is feasible by means of FFR studies (fractional flow reserve by catheterization) or by noninvasive methods, such as myocardial perfusion by cardiac magnetic resonance imaging, ECHO with stress and myocardial perfusion scintigraphy with stress, and, recently, FFR-CT (DeFACTO *Study*), which is the evaluation of coronary artery flow reserve by computed tomography[20].

The quantification of the ischemia severity and length has important prognostic value[16]. In the clinical practice, a significant number of CTA tests with moderate stenosis have been found to need complementary functional tests, such as CMRI or SPECT. This fact has been encouraging the development of noninvasive methods that evaluate the anatomy (stenosis) and myocardial perfusion (ischemia) in a single test[21].

Computed Tomography Myocardial Perfusion Imaging

CTA is a noninvasive method to evaluate obstructive coronary diseases, characterizing the degree of stenosis and the presence of atherosclerotic plaques, evaluating not only the lumen, but also the vessel wall, with plaque characterization. In the literature, detecting significant obstructive coronary diseases (luminal narrowing > 50%) by CT shows a good accuracy with high sensitivity (82% - 99%) and specificity (94% - 98%) compared to ICA[22-25]. In these studies, the high Negative Predictive Value (NPV) of the method (95% - 99%) is relevant, insofar as it is useful to eliminate obstructive coronary disease, which makes of CTA an excellent tool for noninvasive evaluation of coronary arteries. CTA was ultimately validated versus ICA by multicenter clinical studies[26-27].

Technical requirements to perform CTP

The patient's preparation is similar to that necessary in other myocardial perfusion methods with pharmacologic stress, which may use dipyridamole, adenosine or regadenoson (selective A2A adenosine receptor agonist, still unavailable in Brazil for clinical use). Patients should be instructed about the restriction of food with caffeine and/or xanthines, nonselective competitors of the adenosine receptor in the patients to be subject to pharmacological stress. For the injection of contrast and vasodilator, two antecubital venous accesses are necessary, preferably 18 gauge, allowing the infusion at speeds higher than 5 mL/s. Usually the a adenosine (140 mcg/Kg/min) is injected under continuous monitoring over 2 - 3 minutes[26-32], but longer injections of 5 - 6 minutes have already been tested[33-35].

The administration of oral and intravenous beta-blocker should be considered to reach a rate of 60 bpm, in an attempt to mitigate the movement artifacts in the protocols in which the rest phase precedes the stress. Some authors refrain from using it due to the possibility of hiding the ischemia in the myocardial perfusion. However, in accordance with recent studies, no effect in the coronary reserve has been revealed by pharmacological stress studies with SPECT and CTP[35-38]. In view of this, the use of beta-blocker should be considered to facilitate the acquisition of data with better image quality.

Acquisition parameters and methods

CTP usually comprises two phases, namely rest and stress, not necessarily in this order. The main advantage of firstly conducting the rest phase would be the possibility of ruling the stress phase out for patients with coronary arteries without obstructive lesions. In turn, the performance the stress phase before the rest phase would allow a better detection of the myocardial ischemia, with an improved differentiation between ischemic and nonischemic myocardium.

In 320 slice scanners, the image acquisition should be performed with the tube voltage at 120kV, tube current at 300 - 500 mAs (depending on the patient's BMI) resorting to prospective acquisition with coverage of 70% - 95% of R-R interval[27,33,36]. In dual source scanners, several acquisition protocols have been described[26,28-32,34,39,40]. In second-generation dual source scanners, the prospective axial and spiral acquisition in high pitch (flash mode) were used instead of the retrospective acquisition of the first-generation apparatuses. The dynamic acquisition in the shuttle mode (quick movement from the scanner table between two positions covering the entire heart)[28,30,32,39,41-43] is an alternative more and more investigated. Additionally, dual source systems allow performing dual energy CT to evaluate the myocardial perfusion defects[27,34,40], with a tube acquiring 140 kV images, and the other, 80 kV[34,40].

The development of new scanners with multiple detectors allowed the performance of CTP, with radiation doses at quite low levels. The 64-channel scanners generation is limited to a coverage of 4 cm, demanding several gantry rotations to cover the entire heart, demanding 5 - 8 heartbeats and an apnea period of 8 - 10 seconds (radiation dose of up to 16.8 mSv[44]). The new 320 detector row scanners allow a coverage area of up to 16 cm, allowing the evaluation of the entire heart in a single gantry rotation and an apnea of 1 to 2 seconds without the need to move the table (average radiation dose of 5.4 mSv[36]). The second dual source generation has a gantry with two X-ray tubes at a 90 degree angle with two corresponding detectors, resulting in a higher time resolution (75 ms) and spatial resolution of 0.3 to 0.4 mm, allowing a fast acquisition with low heart movements and reducing the artifacts. The acquisition may be performed with table spiral or shuttle modes, and may reach the radiation dose of 1 mS[45], using the high pitch technique.

During the rest phase, 60 to 70 mL of iodinated contrast are administered at 5 mL/s and the image acquisition is performed in keeping with the preset protocol (prospective or retrospective). For the stress phase, the adenosine infusion starts at 140 mcg/Kg/min until the 5th minute, and, in the case of the dipyridamole, a dose of 0.56 mg/kg/min is injected at 4 minutes. Once more, 60 to 70 mL of contrast is administered at 5 mL/s, except for 64-detector row scanners, in which injection should be made at 3 mL/s to keep a higher contrast homogenization in the left ventricle over the entire acquisition. The image acquisition starts when the contrast attenuation at a specific spot reaches a present amount, for instance, 300 HU in the descending aorta. It may also be performed 2 to 4 s after the contrast peak, which is ascertained with the bolus test of 10 to 15 mL followed by 20 mL of saline solution (Figure 1 and Figure 2).

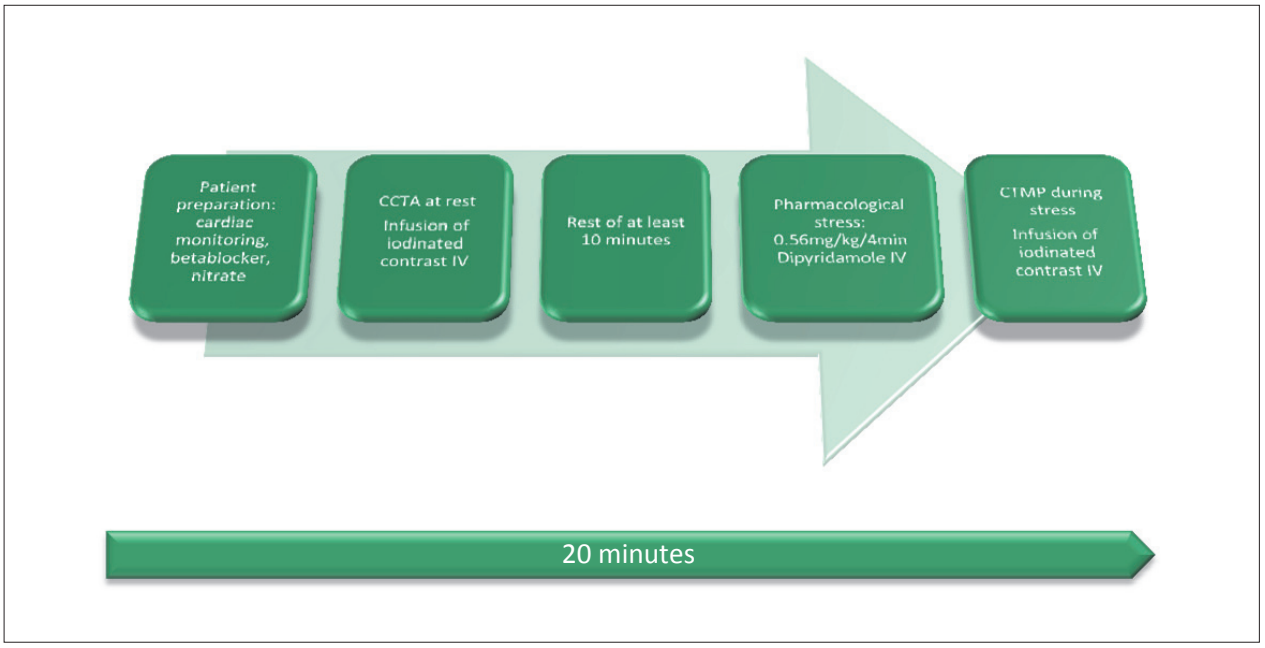

Figure 1 – *CTP protocol with rest phase followed by stress phase.*

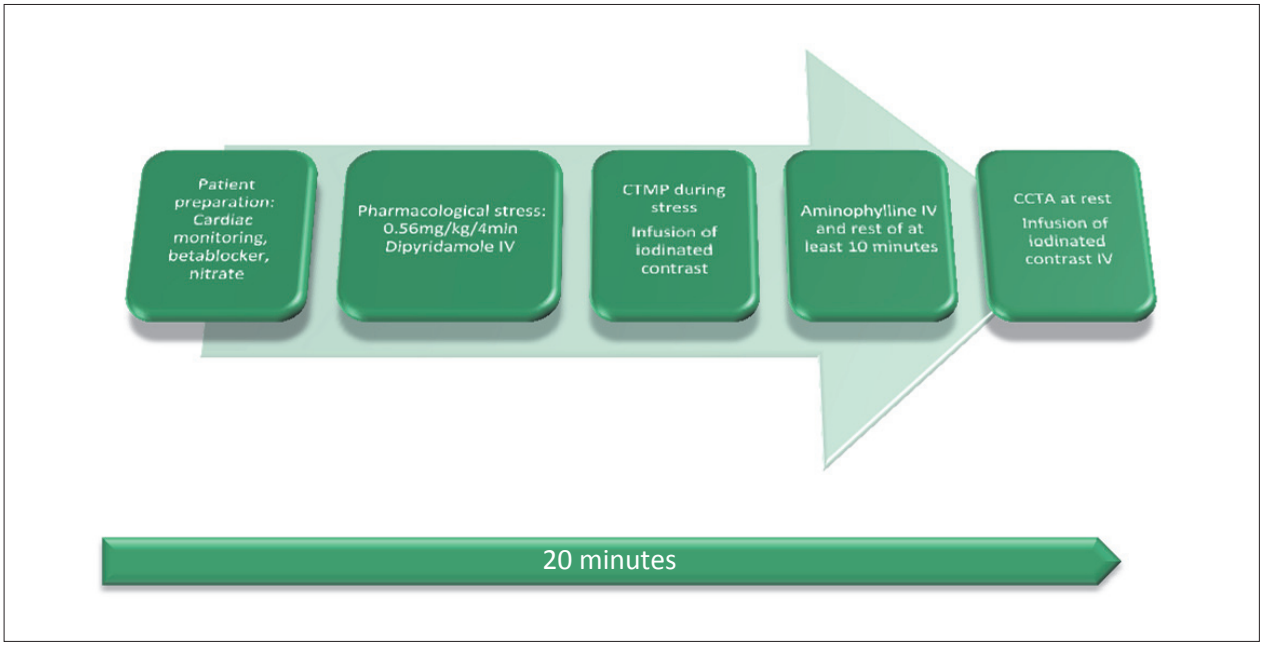

Figure 2 – *CTP protocol with stress phase followed by rest phase.*

Analysis of the images

The detection of myocardial detection is possible, as the iodinated contrast has a property capable of attenuating the X-rays proportionally to the concentration in the myocardium. The images are acquired over the first contrast pass in the coronary arteries and myocardium during rest and stress with vasodilator. In the absence of artifacts, the reversibility or persistence of perfusion defect between stress and rest allows differentiating infarction and ischemia. A third late phase may be performed, allowing the evaluation of myocardial viability (late enhancement).

The analysis of the myocardial perfusion images includes the side-by-side analysis of stress and rest images. The stress-induced myocardial ischemia is defined as the hypoattenuation in

territory compatible with coronary arteries segmentation in images under vasodilator stress, without late enhancement in images of viability or hypoperfusion at the rest phase[30,46]

The qualitative interpretation of the myocardial perfusion has been used in most clinical trials by now, resorting to simultaneous comparison of rest and stress images (Figure 3). The images are generally interpreted using an image adjustment (Window-200/Level-100 or 300/150) and an average thickness of 3 to 5 mm (MPR thick) in short axis view[27,28,30-32] .

Using the 17 segment model of the American Heart Association classifying the segments with presence or absence of perfusion defects is possible, grading them in transmural, if any, > 50% of the myocardium and nontransmural or subendocardial (< 50%), depending on the length of the affected myocardium[28,32,36] . The reversibility defects are graded in each segment as follows: 0 = none; 1 = minimum (up to 1/3 of the myocardium thickness); 2 = partial (1/3 up to 50% of the myocardial thickness); 3 = full[32,36] (> 50% of the myocardial thickness)[47]. All defects are analyzed in multiple phases to ascertain if it is an actual perfusion defect or artifact[33]

Clinical Trials

CTP has been evaluated in a number of centers[21,28,30–33,36,41,44,48-51]. The sensitivity ranges between 79% and 97%, and the specificity, from 72% to 98%, depending on the device used, reference standard, population studies, and if the analysis is per patient, segment or coronary territory. Recent studies evaluated the accuracy of CTP using devices with one or two X-ray sources, with limited longitudinal coverage[21,28,32,44, 48,49].

SPECT was chosen as the standard method in most studies[21,28,32,43,44,48,49,51] given that it allows a high prognostic value if used along with ICA[17] (Table 1 and Table 2). However, in multivessel patients its accuracy is limited as the technique consists in identifying perfusion differences between contiguous myocardial territories, hampering the detection of multivessel diseases. To overcome this methodological limitation, several independent analyses were performed to allow ascertaining the CTP role for multivessel diseases as well. Because of this, recent studies have been choosing methods that are less influenced by the presence of ischemia in contiguous territory, such as CMRI and coronary flow reserve (FFR) as a more appropriated

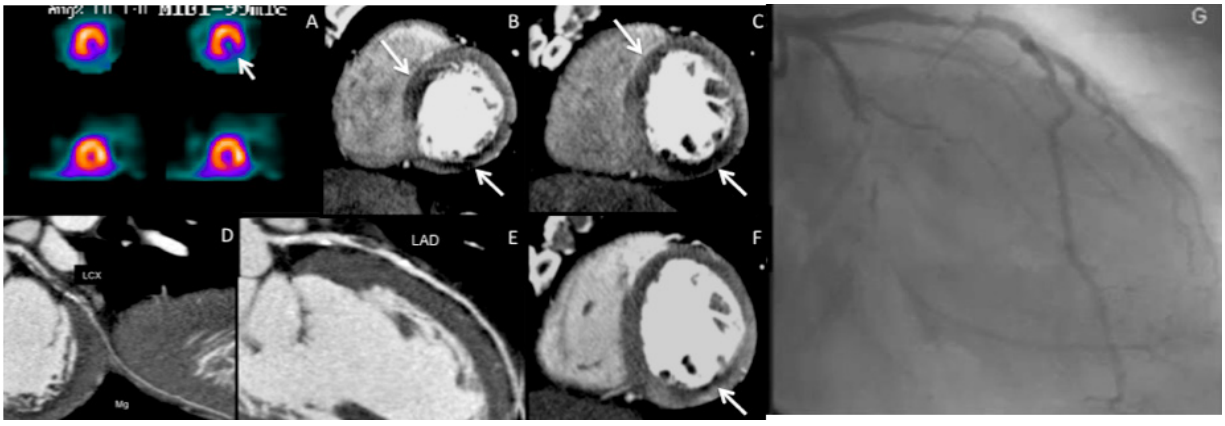

Figure 3 - *CTP model correlating the ischemic area with SPECT and ICA. (A) SPECT: Short axis image of the normal rest perfusion, on the lower line, and presence of inferolateral myocardial perfusion defect (white arrow) after pharmacological stress; (B and C) CTP: Stress hypoperfusion in anteroseptal and inferolateral wall (white walls); (D) Curved reformation image of the circumflex artery with occlusion of the proximal segment; (E) Curved reformation image of the anterior descending artery with important proximal luminal narrowing; (F) CTP: Short axis rest perfusion showing minor inferolateral perfusion defect (white arrow); (G) ICA: Right anterior oblique image showing important luminal narrowing in DA and occlusion of Cx in the middle segment with distal filling via collateral circulation.*

Table 1 – CTP compared to coronary angiography

Author	Number of patients	Scanner	Protocol	Radiation Dose (mSv)	Sensitivity[a]	Specificity[a]	PPV[a](%)	NPV [a](%)
Rocha-Filho et al.	35	*Dual-source* (2x32)	Stress: Retrospective Rest: Prospective	Stress: 9.8 ±4.5 Rest: 2.0±0.7	91	91	86	93
Bamberg et al.	33	*Dual-source* (2x64)	Stress: *"shuttle mode"* Rest: Prospective	Stress: 10.0±2.0 Rest: 3.1±1.0	93	87	75	97
Ko et al.	42	320 detectors	Stress: prospective Rest: prospective	Stress: 5.3±2.2 Rest: 4.8±2.6	68	98	97	77

PPV: positive predictive value; NPV: negative predictive value. [a]: Combination of CTA and CTP to ascertain the diagnostic accuracy to evaluate the vessel. Source: Modified table of Schuhbäck et al.35

Table 2 – CTP compared to the myocardial perfusion scintigraphy

Author	Number of patients	Scanner	Protocol	Radiation Dose (mSv)	Sensitivity	Specificity	PPV (%)	NPV (%)
[a] Cury et al.[21,53]	26	64	Stress: Retrospective Rest: Retrospective	Total: 14.4±2.9	94	78	89	87.5
[b] Cury et al.[21,53]	36	64	Stress: Retrospective Rest: Retrospective	Stress: 3.4±0.3 Rest: 11.6±2.3	CT: 69 SPECT: 64	CT: 89 SPECT: 77	CT: 81 SPECT: 66	CT: 81 SPECT: 76
[c] Wang et al.[47]	30	Dual Source (2x64)	Stress: *"shuttle mode"* Rest: prospective	Stress: 9.5±1.3 Rest: - Total: 12.8±1.6	85	92	55	98
[d] Blank-stein et al.[32]	33	Dual Source (2x32)	Stress: Retrospective Rest: Prospective	Stress: 9.1±3.9 Rest: 2.0±0.6	84	80	71	90

PPV: positive predictive value; NPV: negative predictive value. [a]: Comparison between CTP and SPECT in the analysis per patient. [b]: Comparison between CTP and SPECT in the evaluation per territory, using CTA as reference. [c]: Comparison between CTP and SPECT in the evaluation per segment. [d]: Comparison between CTP and SPECT in the evaluation per affected vessel. Source: Modified table of Schuhbäck et al.[35]

Cury et al.[21,52] compared the pharmacological stress perfusion technique using dipyridamole by 64 detector row CT to evaluate the myocardial ischemia with SPECT. Using obstructive lesions more than 70% diagnosed by ICA as reference for anatomical confirmation and correlation of lesion with myocardial ischemia areas diagnosed by both methods (tomography and scintigraphy), the values of sensitivity, specificity, PPV and NPV for stress perfusion by tomography were 88%, 79%, 66% and 93%, respectively, without significant difference compared to the myocardial scintigraphy data (Table 2).

Magalhães et al.[53] compared the additional value of perfusion under pharmacological stress with dipyridamole by computed tomography with 64 detector rows versus the independent anatomical evaluation by CTA in patients with stents, adopting ICA as reference (≥ 50%). The evaluation of the independent CTA presented sensitivity, specificity, NPV, PPV and accuracy in the territories with stent of 85%, 77%, 87%, 74% and 81%, respectively. After the use of CTP, the diagnostic performance was 88%, 95%, 97%, 81% and 91%, respectively ($p = 0.0292$). In territories with limited or inappropriate evaluation of stent the performance diagnosed by the independent CTA was 83%, 72%, 79%, 76% e 77%, respectively, and, when associated with CTP, reached 87%, 94%, 95%, 85% and 91%, respectively, $p = 0.036$), showing an improvement in the accuracy to detect significant coronary artery stenosis in patients with stent.

Rochitte et al.[54] presented the first international multicenter study, of prospective character, using computed tomography myocardial perfusion imaging (CORE 320 study). This study compared CTA combined with CTP to detect hemodynamically significant stenoses defined by the combination between ICA and SPECT. All patients have been referred to ICA to investigate suspected or known CAD, and previously subject to CTA, CTP and SPECT before ICA. The results showed that CTP improved the diagnostic power of CTA, if seen independently (AUC of ROC curved was increased from 0,82 to 0,87 when resorting to the combination CTA + CTP to detect hemodynamically significant stenosis), especially in individuals without previous CAD, in which the AUC of ROC curve reached 0.93. The study also revealed that CTA + CTP has the same power to identify patients who would need bypass grafting within 30 days after the performance of standard strategy (ICA + SPECT). It also underlined the possibility of evaluating the myocardial anatomy and perfusion by a single test, in a noninvasive manner. Independent ICA detected obstructive CAD in 59% of the patients, although, when associated with SPECT, this was reduced to 38%.

The incremental value of CTP to improve the accuracy of CTA to detect stenoses ≥ 50% in ICA was evaluated in 35 patients with high risk of CAD using MDCT with double source. The authors showed an increase of sensitivity from 83% to 91%; specificity, from 71% to 91%; and ROC curve from 0.77 to 0.90 ($p < 0.005$)[28].

Qualitative and quantitative analysis of ischemia

CTP may be interpreted in a qualitative and quantitative manner. The methods published in the literature for quantitative evaluation include the Transmural Perfusion Ratio (TPR), obtained by static acquisition[21,44] (Figure 4), and the calculation of Fractional Flow Reserve (FFR), obtained by dynamic acquisition[55].

The transmural perfusion ratio is calculated by the average of density in Hounsfield Units of subendocardium divided by the average of the subepicardial density of each myocardial segment defined by the American Heart Association. This ration showed that CTP is capable of detecting and quantifying perfusion defects compared to SPECT, in addition to presenting an excellent accuracy identifying perfusion defects after pharmacological stress and significant coronary artery obstruction by ICA.

The calculation of fractional flow reserve is made by the real time dynamic acquisition, whereby the myocardial iodine attenuation time curve is obtained, differentiating the iodine kinetics in the remote and ischemic myocardial, and obtaining the estimated FFR by mathematical calculation.

FFR presented strong correlation with ischemic territories by SPECT, magnetic resonance imaging and with the presence of significant obstructive coronary artery disease by invasive coronary angiography associated with the fractional flow reserve (FFR)[41].

Both methods are promising tools for the quantitative analysis of CTP but need validation in multicenter studies.

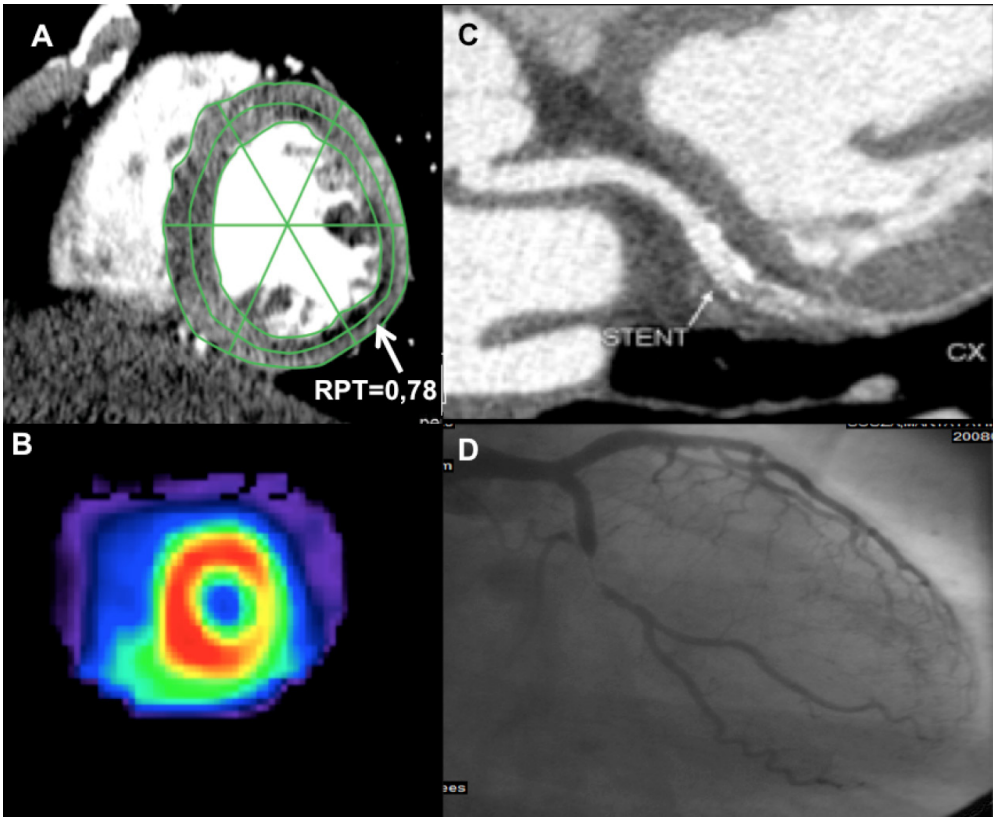

Figure 4 - *Correlation between TPR by MDCT (A), SPECT (B), CTA (C) and ICA. (D), TPR = 0.78 (VR < 0,85) medial inferolateral and significant coronary luminal narrowing of the circumflex artery (> 70%).*

Technical Limitations

The main limitations connected to CTP are the image artifacts, exposure to ionizing radiation and higher volume of contrast injected. The myocardial attenuation may be affected by movement artifacts and beam hardening artifacts, and may overestimate the perfusion defects. In a study by Wang et al.[46], nearly half of the false positive defects was located in the basal segment, but frequently affected by beam hardening artifact, which is the result of the presence of contrast in the left ventricular cavity and aorta[35]. False negative results may be connected to an ineffective dose of vasodilator and the patient's respiratory movement artifacts[29], a small ischemia area or the inappropriate adjustment of width and level. Besides the limitation of the radiation, new acquisition protocols have been diminishing the exposure to effects of the ionizing radiation. Recent studies have been showing that the total dose during CTA/CTP is similar to that of the rest/stress myocardial perfusion scintigraphy (13.8 ± 2.9 mSv and 13.1 ± 1.7 mSv, respectively, p = 0.15)[32,36,56].

Conclusion

The combination of the coronary computed tomography angiogram with computed tomography myocardial perfusion imaging allows the simultaneous identification of the atherosclerotic load, presence of coronary luminal narrowing and possible myocardial narrowing by a fast, practical and reliable method, validated by a multicenter study. By combining anatomical and myocardial perfusion information in a single test, a better therapeutic approach to patients is possible, resulting in an optimized clinical management.

Authors' contribution

Investigation conception and design: Fernandes FV, Cury RC; Data collection: Fernandes FV, Cury RC; Data analysis and interpretation: Fernandes FV, Cury RC; Manuscript drafting: Fernandes FV; Critical review of the manuscript regarding the important intellectual content: Cury RC.

Potential Conflicts of Interest

No relevant potential conflicts of interest.

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Academic Association

This study is not associated with any graduate programs.

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