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ORIGINAL ARTICLE

Coronary Computed Tomography Angiography and C-Reactive Protein in the Evaluation of Coronary Artery Disease

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Abstract

Background: Coronary artery disease (CAD) is the leading cause of death in developed countries. In Brazil, approximately 1.74% of the gross domestic product is spent on cardiovascular diseases. Ischemia tests have a low diagnostic accuracy for patients with intermediate CAD risk, and multidetector computed tomography angiography (MDCTA) may help establish the diagnosis of these patients, despite the cost of this procedure, which is still high for our standards. C-reactive protein (CRP) is increased in cases of systemic inflammation and has been used as a CAD marker.

Objective: To evaluate the correlation of CRP with the presence of atherosclerotic plaques identified on CT angiography.

Methods: Cross-sectional study including 118 patients with intermediate risk of CAD, who underwent coronary MDCTA and CRP measurement from September 2011 to January 2013 in a referral cardiology hospital.

Results: Males comprised about 55% of the sample. CAD, hypertension, and obesity were identified in 68.6%, 76.3%, and 31.8% of the subjects, respectively. We observed that patients with increased CRP levels had a 2.9-fold higher chance of presenting CAD on MDCTA (p = 0.016).

Conclusion: Individuals with altered CRP are more likely to present CAD diagnosed by MDCTA and have higher CRP values than patients without CAD. CRP, along with other risk factors, may represent a relevant predictive element in the diagnosis of CAD in MDCTA, or in situations in which MDCTA is not feasible. (Int J Cardiovasc Sci. 2016;29(5):338-347)

Keywords: Coronary Artery Disease / mortality; Multidetector Computed Tomography / methods; Atherosclerosis; Thrombosis, C-Reactive Protein.

Introduction

Cardiovascular disease is the leading cause of death in the world. In a single year, 17.5 million deaths occur due to cardiovascular diseases, of which 7.4 million are secondary to coronary artery disease (CAD). Only in Brazil, approximately 1.74% of the gross domestic product (GDP) is directed to expenses with cardiovascular diseases.[1,2,3]

Multidetector computed tomography angiography (MDCTA) is a diagnostic method for patients with an intermediate CAD risk.[4] This method has a high diagnostic accuracy (sensitivity of 91 to 99% and specificity of 74 to 96%) and a high negative predictive value (between 96% and 100%). It allows fast and noninvasive obtainment of images of the lumen and walls of the coronary arteries, in addition to quantifying the diameter and analyzing the composition of atheroma

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plaques, distinguishing calcified from noncalcified ones.[4-6] In addition, MDCTA shows a better performance over functional tests in identifying obstructive disease and is increasingly applied in clinical practice due to recent technological advancements in multidetector computed tomography, which further enhanced the temporal and spatial resolution of the images.[6]

C-reactive protein (CRP) is an acute phase protein produced by hepatocytes that increases in systemic inflammation. CRP synthesis is regulated by increased concentrations of the cytokine interleukin-6 (IL-6).[8]

The mechanism responsible for the association of CRP with cardiovascular diseases may be attributed to the fact that the inflammatory process contributes to the development of the atheromatous plaque in the endothelial cells of the vessel, in addition to facilitating the rupture of the atherosclerotic plaque, causing thrombolysis.[8]

In addition to CRP, other possible markers of CAD and predictors of cardiovascular events that have already been tested include fibrinogen, the serum amyloid protein, cytokines, and peripheral blood cells involved in inflammation, such as leukocytes, lymphocytes, and monocytes. However, serum CRP is the most promising marker in helping establish the diagnosis of CAD, in addition to being easily measured, and having high sensitivity and accuracy and easy reproducibility.[9,10]

Methods

Casuistry

This is a cross-sectional study, conducted from September 2011 to January 2013 at a referral cardiology center including individuals selected or referred from the emergency department, who underwent coronary MDCTA and CRP determination.

The sample comprised patients referred by their cardiologists with a clinical indication for MDCTA. The determination of the intermediate risk was based on the Framingham score, considering a risk of 10 to 20% of myocardial infarction, angina, or death from cardiac causes during an interval of 10 years (a value that tends to be overestimated in Latin American countries).[11] We excluded patients weighing more than 120 kg due to the weight limitation of the computed tomography table and with a creatinine clearance < 50 mL/min due to nephrotoxicity caused by the iodinated contrast.

The study was approved by the ethics and research committee under protocol number CAAE 1818.0.000.107-06.

Multidetector computed tomography angiography

We used a protocol divided into two phases to acquire the MDCTA images for evaluation of the coronary arteries. First, we performed an acquisition named calcium score (CS) without using contrast and coupled with the electrocardiogram. Soon after that, we performed the MDCTA using contrast media.[12]

Initially, we obtained anteroposterior and lateral scout images of the chest to select the axial slices for the test. The beginning of the block was delimited at the bifurcation of the trachea and the end at the inclusion of the cardiac silhouette, including the final portion of the diaphragm in order to scan the entire cardiac area. After delimitating the area to be studied using the field of view (FOV), we performed prospective acquisitions.

In order to avoid image distortion, the heart rate must be ≤ 65 bpm, since the X-rays must be emitted in synchrony with the patient's cardiac cycle. In patients with a heart rate above 65 bpm, we administered atenolol 25–100 mg.

In the second stage of the protocol, we obtained coronary angiotomography images using the CS parameters to delimitate the FOV, with a voltage of 120 KV and amperage of 400 milliamperes.

With the patient still monitored on the computed tomography table, we injected approximately 1.5 mL/Kg of intravenous iopamidol, a nonionic iodinated contrast, at a concentration of 370 mg/mL (*Ultravist*® 370, Bayer HealthCare and Pharmaceuticals, Berlin, Germany), at a rate of 4.5 mL/s. Approximately 15 seconds later, the patient performed an exercise of apnea lasting about 20 seconds during the acquisition to minimize image motion artifacts.

During MDCTA image acquisition, the variation in heart rate must not exceed 10% of the baseline rate. The equipment uses as a reference the monitored heart rate values and determines the necessary parameters for image acquisition such as helical pitch (relationship between the table movement distance during a 360º rotation of the X-ray tube, slice thickness, and the number of detector elements), the speed rotation of the X-ray tube, and the total time of image acquisition, aiming to achieve the best possible temporal resolution.[13]

The images generated were sent to a workstation for analysis of the coronary arteries by experienced observers. Patients presenting any type of atherosclerotic plaque on MDCTA were diagnosed as having CAD.

C-Reactive Protein Measurement

Peripheral venous blood was collected in dry sterile tubes (BD Vacutainer SST II Advance) and centrifuged at 3,000 rpm for 10 minutes. The separated serum was used for CRP measurement.

Quantitative CRP measurement was performed with the biochemical reagent CRP *VITROS Chemistry Products*, CRP VITROS slides, and the kit Calibrator 7 *Vitros Chemistry Products* in the chemical systems VITROS 250/350/950/5,1 FS and 4600 and in the integrated system VITROS 5600® (Johnson & Johnson).

For CRP measurement, we used a sandwich-type enzyme immunoassay. The sensitivity of the test is 0.5 mg/dL and the samples that reached this concentration were further analyzed with high-sensitivity CRP (hs-CRP).

Quantitative measurement of hs-CRP concentration was performed with an immunochemical test using the reagents of the kit hs-CPR *VITROS Chemistry Products* and the chemical system VITROS 5,1 FS, in the equipment *VITROS 5600*® (Johnson & Johnson).

The kit reagents are available in a liquid form and are ready for use. We used spectroscopy to perform the measurements and determined the sample turbidity at 660 nm.

Statistical analysis

The statistical analysis was performed using the software Stata, version 14.1. The data are expressed as mean and standard deviation for numerical variables and absolute number and percentage for categorical variables. In comparisons between quantitative variables, we used Student's *t* test or the Mann-Whitney test for non-normal distributions. To test the assumption of normality in the distribution, we performed the Shapiro-Wilk test. For categorical variables, we used the chi-square test or Fisher's exact test. P values < 0.05 were considered statistically significant. To assess the agreement of the methods, we used the kappa coefficient (kappa statistics estimate differences between the calculated and expected agreements).

Models predictive of positive findings on angiotomography were evaluated, and calibration tests (Hosmer-Lemeshow) and ability to discriminate (area under the ROC curve) were applied. We chose to select a prediction model of positive CAD on angiotomography which, in addition to being parsimonious and having an easy clinical application, would result in post-estimate adequacy with satisfactory calibration and discriminative ability. The model with the best adequacy included among the predictors were the variables gender, age, and CRP (which was evaluated dichotomously as altered or normal). Using multiple logistic regression, we calculated the predictors' odds ratios, 95% confidence intervals (95%CI), and p values.

We developed a nomogram to represent graphically the prediction model and, at the same time, provide scores to estimate the probability of an angiotomography positive for CAD in a sample with a similar population profile.

Results

Clinical characteristics of the study population

Of the 118 patients who underwent coronary MDCTA and CRP measurement, the mean age was 59 ± 10.51 years. In all, 55.1% of the patients were males and 76.3% had hypertension (Table 1).

Results of multidetector computed tomography angiography and C-reactive protein

Among the patients undergoing MDCTA, 81 (68.6%) were identified as having CAD according to the presence of atheroma plaques in any of the segments of the coronary arteries. We observed no significant differences regarding gender or occurrence of diabetes mellitus (DM) and obesity when we compared patients with and without plaques. However, the parameters dyslipidemia (77.2%, $p = 0.002$), hypertension (82.7%, $p = 0.015$), use of statins (73.1%, $p = 0.026$), and use of aspirin (58.0%, $p < 0.001$) were more frequent in the CAD group (Table 2).

The CRP concentration in all individuals in the study ranged from 0.02 to 5.0 mg/dL, showing an important positive asymmetry (3.06) and kurtosis (13.69), with a non-normal distribution on the Shapiro-Wilk test ($p < 0.001$). After categorizing the CRP values into two levels (normal and altered), we analyzed their distribution according to gender (Figure 1). We observed that 59.3% ($n = 70$) of the patients had altered CRP values (≥ 0.3 mg/dL). Comparing the groups with normal and altered CRP, we observed no differences in regards to the occurrence of DM, dyslipidemia, hypertension, obesity, and use of statins. However, we observed significantly lower rates of altered compared with normal CRP

among men (43.4%, p = 0.021). In contrast, there were significantly higher rates of altered versus normal CRP among patients using aspirin (56.8%, p = 0.042) (Table 2).

The mean CRP concentration was 0.76 ± 0.55 mg/dL in patients with plaques and 0.48 ± 0.21 mg/dL among those without plaques (p = 0.026).

Table 1
Biodemographic data of patients who underwent multidetector computed tomography angiography and measurement of C-reactive protein

Biodemographic Data	Values	N
Mean age (years)	59.2 ± 10.5	118
Male gender	55.1%	65/118
Ethnicity		
White	72.9%	86/118
Black	18.6%	22/118
Dark-skinned	6.8%	8/118
Asian	1.7%	2/118
Hypertension	76.3%	90/118
Dyslipidemia	66.1%	78/114
Obesity	31.8%	34/107
BMI (kg/m²)	27.35 ± 5.52	118
Diabetes	22.9%	27/113
Statin use	54.2%	64/97
Aspirin use	38.1%	45/99

BMI: body mass index. The values are represented as mean ± standard deviation. The frequencies are represented as percentage.

Table 2
Association between clinical characteristics and coronary artery disease (CAD) on multidetector computed tomography angiography or altered C-reactive protein values

Variables	N	CAD	Without CAD	p	Altered CRP	Normal CRP	p
Male gender	65/118	45 (55.6%)	20 (54.1%)	0.879	23 (43.4%)	42 (64.6%)	0.021
Hypertension	90/118	67 (82.7%)	23 (62.2%)	0.015	43 (81.1%)	47 (72.3%)	0.262
Dyslipidemia	78/114	61 (77.2%)	17 (48%)	0.002	39 (76.5%)	39 (61.9%)	0.096
Obesity	34/107	24 (33.3%)	10 (28.6%)	0.620	23 (37.7%)	11 (23.9%)	0.129
Diabetes	27/113	22 (28.2%)	5 (14.3%)	0.109	13 (26.0%)	14 (22.2%)	0.640
Statin use	64/97	49 (73.1%)	15 (50.0%)	0.026	31 (72.1%)	33 (61.1%)	0.257
Aspirin use	45/99	40 (58.0%)	5 (16.7%)	< 0.001	25 (56.8%)	20 (36.4%)	0.042

CRP: C-reactive protein. The values are represented as percentage. P value obtained with the chi-square test for association measures.

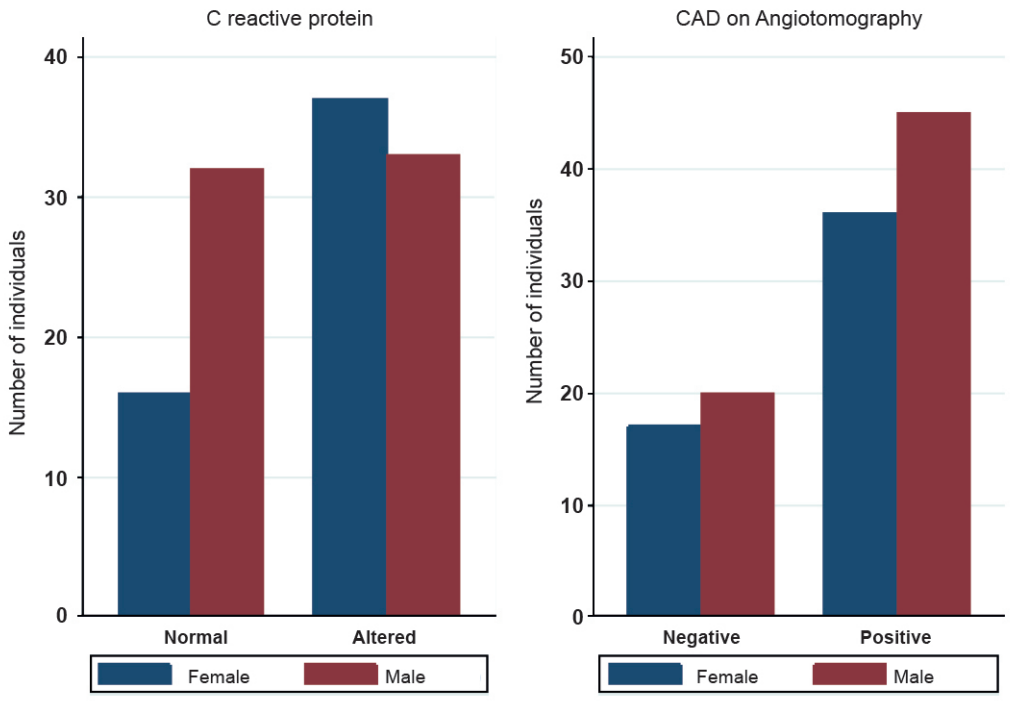

Figure 1
Analysis of the distribution pattern of the variables C-reactive protein (CRP) and coronary artery disease (CAD) on angiotomography according to gender. There was a higher frequency of altered CRP in women and a higher frequency of angiotomographic reports compatible with CAD in men.

Among patients with plaques, women had a higher mean age (64 ± 10.7 years, p = 0.01), whereas in the group with altered CRP, the mean age was higher among men (63 ± 10.8 years, p = 0.003) (Table 3).

The analysis of the distribution pattern of the variables "CRP" and "CAD on angiotomography" according to gender (Figure 1) showed a higher frequency of altered CRP in women and increased frequency of angiotomographic reports compatible with CAD in men. The kappa agreement index was 0.21 (Table 4).

The analysis of contingency tables showed a higher odds ratio in patients with altered CRP (odds ratio = 2.9, 95%CI = 1.22 – 6.97, p = 0.016).

Although the male gender showed a higher odds ratio (1.88), this finding had no statistical significance (95%CI = 0.76 – 4.66, p = 0.171), which may have occurred, among other factors, from the reduced sample size.

Significant odds ratios were observed in both age (1.07, 95%CI = 1.03 – 1.12, p = 0.001) and CRP (2.92, 95%CI = 1.22 – 6.98, p = 0.016). The Hosmer-Lemeshow test indicated satisfactory model adequacy (p = 0.57) and area under the ROC curve (0.74), which showed to be regular in terms of prediction (Figure 2).

Additions of covariates did not increase the predictive ability of the model significantly and incurred in a reduction of power, possibly due to the sample size. In contrast, analyses after removal of single or combined covariates resulted in models of lower adequacy; this was verified by a reduction in the area under the ROC curve, which ranged between 0.61 and 0.73.

The nomogram in Figure 3 displays a visual representation of the predictive model adopted in this study. From values extracted from the study sample, we developed some examples with a likelihood of a positive CAD as an outcome dependent on the predictors:

1) 42 years (5 points) + male gender (1 point) + altered CRP (1 point) = 7 points = almost 50% probability.
2) 67 years (8 points) + altered CRP (1 point) + male gender (1 point) = 10 points = 85% probability.
3) 42 years (5 points), female gender and normal CRP = 5 points = 20% probability.

Table 3
Results of multidetector computed tomography angiography and C-reactive protein

CRP versus CAD	N	Values	p
CRP in the group without CAD (mg/dL)	37	0.48 ± 0.21	
CRP in the group with CAD (mg/dL)	81	0.76 ± 0.55	0. 026
Age of men with CAD (years)	45	59 ± 8.9	
Age of women with CAD (years)	36	64 ± 10.7	0.01
Age of men with altered CRP (years)	36	63 ± 10.8	
Age of women with altered CRP (years)	37	56 ± 9.8	0. 003

CRP: C-reactive protein; CAD: coronary artery disease. The values are represented as mean ± standard deviation.

Table 4
Diagnostic agreement of coronary artery disease between multidetector computed tomography angiography and C-reactive protein using the kappa index

CRP	Presence of CAD on MDCTA	Absence of CAD on MDCTA	Total	Observed kappa	p
Altered (≥ 0.3 mg/dL)	54	16	70	0.21	0.016
Normal (< 0.3 mg/dL)	27	21	48		
Total	81	37	118		

CRP: C-reactive protein; MDCTA: multidetector computed tomography angiography; CAD: coronary artery disease.

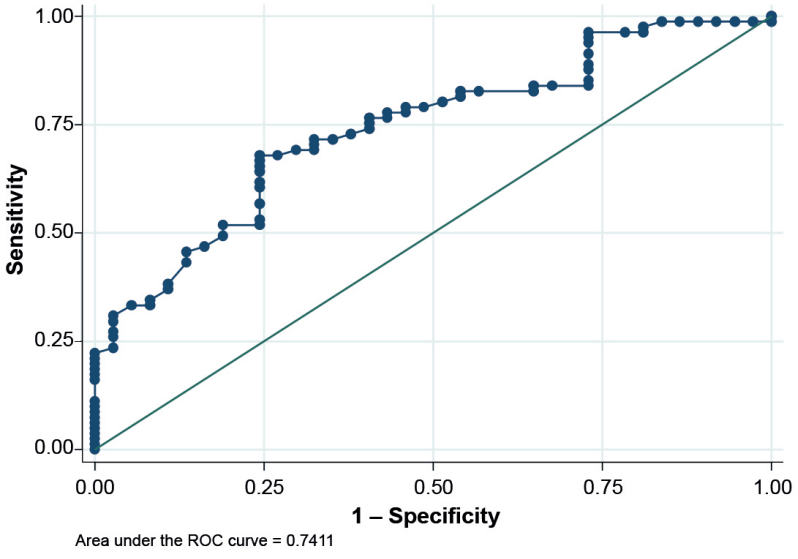

Figure 2
ROC curve (including the area under the curve) in the prediction of an angiotomography positive for coronary disease according to age, gender, and presence of altered CRP.

Through a visual analysis of the nomogram (Figure 3), we observed that an individual's age was the major predictor of the presence of plaque when compared with gender and CRP concentration. Similarly, the classification based on altered CRP values contributed to a higher score than the gender difference.

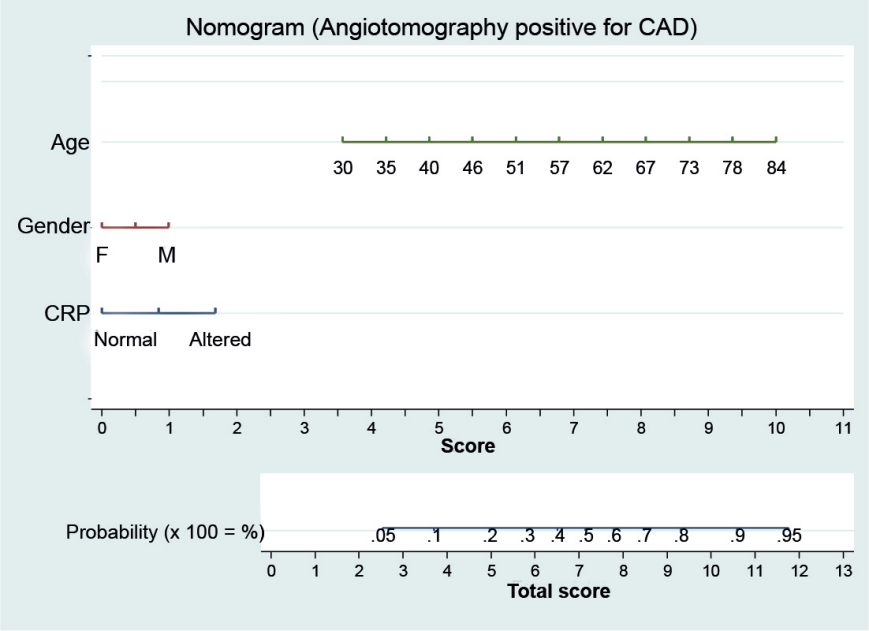

Figure 3
Nomogram with a formula for the calculation of prediction of positive angiotomography for coronary disease, according to age, gender, and presence of altered CRP.

Discussion

Our results showed a correlation between CRP concentration and CAD diagnosed by MDCTA in the study population. This finding is consistent with several studies in the literature that show altered CRP as an important marker of CAD.[14,15,16]

A study conducted in 450 individuals in Iran (284 patients with documented CAD and 166 healthy individuals) classified a CRP value > 0.3 mg/dL as an independent risk factor for CAD (odds ratio 3.46, $p < 0.001$) when compared with the absence of CAD; this was similar to our findings, which were also significant. As in our study, women also had higher CRP concentrations.[17]

Dyslipidemia, hypertension, DM, and obesity are the most described risk factors for CAD in the literature.[18,19] In the individuals analyzed in our study, hypertension and dyslipidemia showed significantly increased frequencies in patients with CAD diagnosed by MDCTA. However, the frequency of DM and obesity was not significantly increased in these patients. The number of diabetic patients assessed with the MDCTA and CRP measurement was small, which may have interfered with the results.

The occurrence of obesity and CAD was not significantly associated with altered CRP.

A study conducted in Québec, Canada, showed increased CRP concentrations in obese individuals.[20] This may be explained by the association of the adipose tissue with IL-6 synthesis, a proinflammatory cytokine that stimulates the hepatocytes to produce CRP.[7,20] The exclusion of obese individuals from the present study may explain the lack of significance in regards to obesity and CAD diagnosed by MDCTA.

In a study conducted by Lima et al., patients with both hypertension and type 2 DM presented CRP levels above 0.3 mg/dL; however, when both diseases were analyzed separately, they no longer showed a significant correlation with increased CRP levels.[21]

According to the Air Force/Texas Coronary Atherosclerosis Prevention Study, the use of statins decreases directly the levels of CRP.[22] However, in the present study, there were no significant differences regarding the concentration of CRP among patients who did and did not use statins.

We demonstrated a higher CRP concentration in women; this corroborates the findings of a study conducted in Minas Gerais in 536 individuals (50.37% men) which also found a higher CRP concentration in women.[23] In one analysis including 6101 participants in the Dallas Heart Study, women showed significantly higher CRP concentrations than men.[24]

In 2009, the National Academy of Clinical Biochemistry Laboratory published guidelines on biomarkers for primary prevention of cardiovascular disease. According to the guidelines, CRP should not be measured in the general population as a way of determining the occurrence of cardiovascular disease; it should, rather, only be measured to assist in stratifying individuals with an intermediate risk of CAD and in deciding whether or not statins should be implemented as a primary prevention measure.[15] Coronary angiotomography is recommended in individuals with low and intermediate risk with a class IIa recommendation, and presents high sensitivity and specificity to exclude the disease.[4]

According to recent studies, MDCTA has a better diagnostic performance to identify obstructive CAD when compared with functional tests. In the PROMISE study, individuals underwent MDCTA and stress tests and were later referred to cardiac catheterization (the gold-standard test for the diagnosis of CAD). Overall, 72.1% of the individuals who had previously undergone MDCTA presented obstructive CAD, while only 47.5% of those who underwent stress testing presented obstructive CAD identified on cardiac catheterization, thus indicating a higher accuracy of MDCTA.[25]

We observed in our study that individuals with increased CRP concentrations had a greater chance of presenting CAD on MDCTA. CRP measurement is a low-cost, easily accessible method that can assist other methods in stratifying and diagnosing CAD when MDCTA is not feasible.

According to European and American guidelines, CRP may be useful in patients with documented CAD as an independent marker of prognosis of death, myocardial infarction, and restenosis after percutaneous coronary intervention. In contrast, the implementation of interventions for secondary prevention with proven efficacy should not rely on CRP concentrations.[8,26]

Among the limitations of our study, we should mention the small sample size, which prevents the insertion of a greater number of covariates. Also, the dichotomization into "normal" and "altered" in the analysis of angiotomography and CRP findings, which despite providing a model that may be better understood by clinical cardiologists, foregoes the possibility to evaluate the effect of these predictors in a wide range of values.

This was a cross-sectional study, which does not allow a formulation of causal hypotheses. Therefore, we are unable to interpret the association between high CRP and angiotomography compatible with CAD as a cause-and-effect relationship in the sample or in the target population.

Conclusion

The agreement index between angiotomography and CRP reached mild, but statistically significant levels. Individuals with CRP classified as "altered" have a greater chance of presenting CAD diagnosed by MDCTA when compared with individuals with a CRP classified as "normal". This suggests that CRP categorization along with other risk factors and ischemia tests or in situations in which MDCTA is not feasible, represents a relevant predictive element for the diagnosis of CAD.

Author contributions

Conception and design of the research: Gabriel FS, Oliveira JLM. Acquisition of data: Gabriel FS, Oliveira JLM. Analysis and interpretation of the data: Gabriel FS, Almeida-Santos MA, Hirata TDC, Oliveira JLM. Statistical analysis: Gabriel FS, Almeida-Santos MA, Oliveira JLM. Writing of the manuscript: Gabriel FS, Almeida-Santos MA, Hirata TDC, Hirata MH, Pinto IMF, Sousa ACS, Mota FBS, Oliveira DP, Oliveira JLM. Critical revision of the manuscript for intellectual content: Gabriel FS, Almeida-Santos MA, Hirata TDC, Hirata MH, Pinto IMF, Sousa ACS, Mota FBS, Oliveira DP, Oliveira JLM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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