Prognosis of Non-Significant Coronary Atherosclerotic Disease Detected by Coronary Artery Tomography

Marcio Vinícius Lins Barros[1,2], Maria do Carmo Pereira Nunes[3], Bruna Pinto Siqueira[1], Carolina Camargos Braichi Guimaraes[1], David Filipe Silva Cruz[1], Leiziane Assunção Alves Guimaraes[1], Maicom Márcio Perígolo Lima[1], Maria Helena Albernaz Siqueira[2]

Faculdade de Saúde e Ecologia Humana[1], Vespasiano, Minas Gerais; Hospital Materdei[2]; Faculdade de Medicina da UFMG[3], Belo Horizonte, Minas Gerais - Brazil

Abstract

Introduction: Although studies have shown high diagnostic accuracy of coronary tomography (CT) in detecting coronary artery disease (CAD), data on the prognostic value of this method in patients with no significant coronary obstruction are limited.

Objective: To evaluate the value of CT in predicting adverse events in patients with suspected CAD and no significant coronary obstruction.

Methods: We prospectively evaluated 440 patients between January 2008 and July 2013 by MDCT, diagnosed with no significant obstruction or no atherosclerotic coronary obstruction with an average follow-up of 33 months. The outcomes evaluated were: cardiac death, myocardial infarction, unstable angina associated with hospitalization or coronary artery bypass grafting.

Results: Of the 440 patients studied, 295 (67%) were men with mean age 55.9 ± 12.0 years. Non-significant obstruction was found in 152 (35%) of the patients and there were 49 (11%) outcomes. In the multivariate analysis using the Cox regression model, the predictors of clinical outcomes were non-significant obstruction on CT (hazard ratio 3.51; 95% CI 1.73 — 7.8; p <0.01), age and hypertension. Non-significant obstruction on CT was associated with adverse clinical outcomes and survival analysis showed a significant difference (log-rank 24.6; p <0.01) in predicting these outcomes.

Conclusion: The detection of non-significant atherosclerotic obstruction by CT was associated with the presence of adverse events in patients with suspected CAD, which may prove useful in the risk stratification of these patients. (Arq Bras Cardiol: Imagem cardiovasc. 2015;28(3):169-174)

Keywords: Coronary Artery Disease/mortality; Atherosclerosis/mortality; Multidetector Computed Tomography/utilization.

Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality in Brazil and in the world[1]. Coronary atherosclerosis may develop progressive intraluminal stenosis or rupture, with thrombus formation and abrupt occlusion of the coronary artery, causing acute myocardial infarction, unstable angina, or death. Therefore, plaque instability may be related to acute coronary events, regardless of the degree of obstruction[2-4].

Coronary tomography (CT) is a non-invasive imaging diagnosis technique, allowing the detection of atherosclerotic plaques and different degrees of coronary stenosis[5-8]. However, the importance of CT in predicting adverse events in patients with non-significant coronary obstruction is still unclear[9].

The objective of this work was to study, among patients with suspected CAD, who underwent CT, the incidence of adverse events among patients with non-significant atherosclerotic obstruction compared to patients with no evidence of atherosclerotic obstruction.

Material and Methods

Study population

From January 2008 to July 2013, 635 patients were evaluated in a cohort of prospective data collection, with suspected CAD undergoing CT. The indications for CT included evaluation of chest pain, positive result of the stress test, asymptomatic patients with two or more risk factors, abnormal scintigraphy and other causes (abnormal resting ECG and other symptoms of heart disease). Informed consent was obtained from all patients and the study was submitted and approved by the ethics committee of the institution. From the initial sample, 21 patients were

Mailing Address: Marcio Vinicius Lins Barros •
Rua Paracatu, 1451, Postal Code 30180091, Belo Horizonte, MG - Brazil
E-mail: marciovlbarros@gmail.com
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excluded for indication of post-CABG evaluation, 29 for post-angioplasty evaluation and 145 patients with significant coronary obstruction on MDCT, making up a final sample of 440 patients.

Patient data on cardiac risk factors were obtained by questionnaire on admission. Hypertension was considered as documented history of high blood pressure or treatment with antihypertensive medications. Diabetes mellitus was defined as a history of diabetes or use of hypoglycemic drugs. Dyslipidemia was determined as a history of this disease or current treatment with lipid-lowering drugs. Current smoking or cessation of smoking within three months from the test were diagnosed as smoking. Family history of coronary artery disease was defined as the presence of CAD in first-degree relatives under 55 (men) or 65 (women) years of age. Exclusion criteria were: patients who underwent MDCT and diagnosed with significant obstruction, history of known CAD, acute coronary syndrome, cardiac arrhythmia, pregnancy, allergy to iodinated contrast and kidney failure, in addition to patients who did not accept the collection of prospective information or did not sign the informed consent form.

Clinical outcomes were obtained by telephone interview and were classified as the occurrence of: 1) cardiac death; 2) myocardial infarction; 3) unstable angina associated with hospitalization; or 4) revascularization.

Coronary tomography

The device used was 64-channel CT scanner (Aquilion, Toshiba Medical Company, Japan), and the images of the entire heart were obtained in apnea 6-8 s, with venous infusion of 85-90 mL of iodinated contrast (Iopamiron 350) in infusion pump at a rate of 5 mL/s. Automatic contrast detection ROI was positioned in the descending aorta (150 HU), initiating the acquisition of images. Patients with heart rate higher than 70 bpm without contraindications received 15 mg of intravenous metoprolol. The coronary arteries were divided into 17 segments. Segments were evaluated for the presence of any atherosclerotic plaque, defined as ≥ 1 mm^2 structures within and/or adjacent to the light of the coronary artery. Patients without calcium or coronary plaques on CT were considered normal, with an abnormal CT defined as the presence of any coronary plaque. Non-significant obstructive lesion was defined as luminal narrowing < 50%. The percentage of the coronary artery lumen obstruction was defined by comparing the luminal diameter of the obstruction compared to the lumen diameter immediately proximal to the plaque.

Statistical analysis

The demographic and clinical characteristics of the study population were expressed as numbers and percentages for categorical variables; as mean and standard deviation for parametric continuous variables. The comparison between the two groups of patients was done by chi-square test for categorical variables and by Student's t test for continuous variables. To satisfy the assumption of independence of events, the recurrence of cardiac events in a participant was not included in the analysis.

The Cox regression model was used to assess the value of clinical variables and the presence of plaques on CT in predicting cardiac events. Initially, univariate analysis of clinical characteristics and variables and by MDCT was performed to identify potential predictors. Hazard ratios were calculated with 95% confidence interval as an estimate of the relative risk associated with a particular variable. Subsequently, multivariate analysis was performed including all the variables selected in the univariate analysis. Survival analysis was expressed by Kaplan-Meier plot and the p-value of curves was compared using the Log Rank Test. Statistical analyses were performed using the software Epi Info and SPSS (version 18.0, SPSS Inc., Chicago, Illinois) and $p < 0.05$ was considered statistically significant.

Results

The study included 440 patients, 295 (67%) men, mean age 55.9 ± 12.0 years. The general characteristics of the patients are shown in Table 1. The indications for

Table 1 – Basal characteristics of the study population according to the occurrence of coronary events

	Patient with event (n = 49)	Patients without event (n = 391)	Hazard ratio (95% CI)	P value
Age	61.2 ± 11.6	55.3 ± 11.9	1.04 (1.01 – 1.06)	< 0.01
Male sex (n/%)	35 (71)	261 (67)	0.84 (0.45 – 1.56)	0.57
Smoking (n/%)	16 (33)	112 (29)	1.24 (0.68 – 2.26)	0.49
Systemic arterial hypertension n(%)	32 (67)	196(51)	2.00 (1.09 – 3.64)	0.02
Diabetes mellitus n(%)	11 (23)	58 (15)	1.82 (0.93 – 3.58)	0.08
Dyslipidemia n(%)	33 (69)	216 (56)	1.67 (0.91 – 3.08)	0.10
Family history n(%)	28 (58)	229 (59)	0.99 (0.56 – 1.76)	0.97
Physical inactivity n(%)	14 (29)	149 (38)	0.69 (0.37 – 1.28)	0.24
TC n(%)	32 (65)	120 (31)	3.97 (2.20 - 7.14)	< 0.01

NYHA: New York Heart Association; TC: tomografia coronárias com obstrução não significativa.

the MDCT tests were: evaluation of chest pain in 134 (30%) patients, positive results of the stress test in 81 (18%) patients, asymptomatic patients with two or more risk factors in 77 (18%) patients, abnormal scintigraphy in 94 (21%) patients, other causes in 54 (12%) patients. Coronary plaques with no clinically significant obstruction were observed in 152 (35%) patients from the entire sample, including 135 (31%) patients in the anterior descending artery, 76 (17%) patients in the coronary artery, 61 (14%) patients in the circumflex artery, and in some patients, obstruction was observed in more than one artery. The average duration of the clinical study follow-up was 33 months (3-67 months variation). Follow-up was conducted in 398 patients (90.5%). In this period, there were 49 (11%) events. Only adverse clinical outcomes occurring after three months of follow-up at least were selected. Three patients died from cardiac etiology, 34 patients underwent coronary artery bypass grafting, 6 patients manifested ACS and 6 patients had unstable angina requiring hospitalization. Revascularization decision was based on worsening of angina and/or the presence of ischemia in non-invasive tests. Table 1 presents the univariate analysis of the clinical characteristics of the study population. Among the variables analyzed, non-significant obstruction on CT, age, dyslipidemia, diabetes and hypertension were included in the multivariate analysis. Table 2 shows that, on multivariate analysis, independent predictors of adverse cardiac events ($p < 0.05$) were non-significant obstruction on MDCT and hypertension, with Hazard ratio of 3.51 and 3.49, respectively. In Figure 1, the Kaplan-Meier curve showed significant difference (log-rank, $x^2 = 24.6$; $p < 0.01$) in predicting adverse cardiac events among patients with non-significant obstruction and no obstruction on CT.

In our study, the presence of atherosclerosis demonstrated by CT in patients with non-significant obstructive lesions remained as a predictor of adverse clinical outcomes (hazard ratio 3.51; confidence interval of 95% 1.73 — 7.8; $p < 0.01$).

Table 2 – Multivariate analysis by the Cox regression model for predicting cardiac events

Variable	Hazard ratio	95% CI	P value
Systemic arterial hypertension	3.49	1.47 - 8.24	< 0.01
CT with no significant obstruction	3.51	1.73 - 7.08	< 0.01

CT: Coronary tomography.

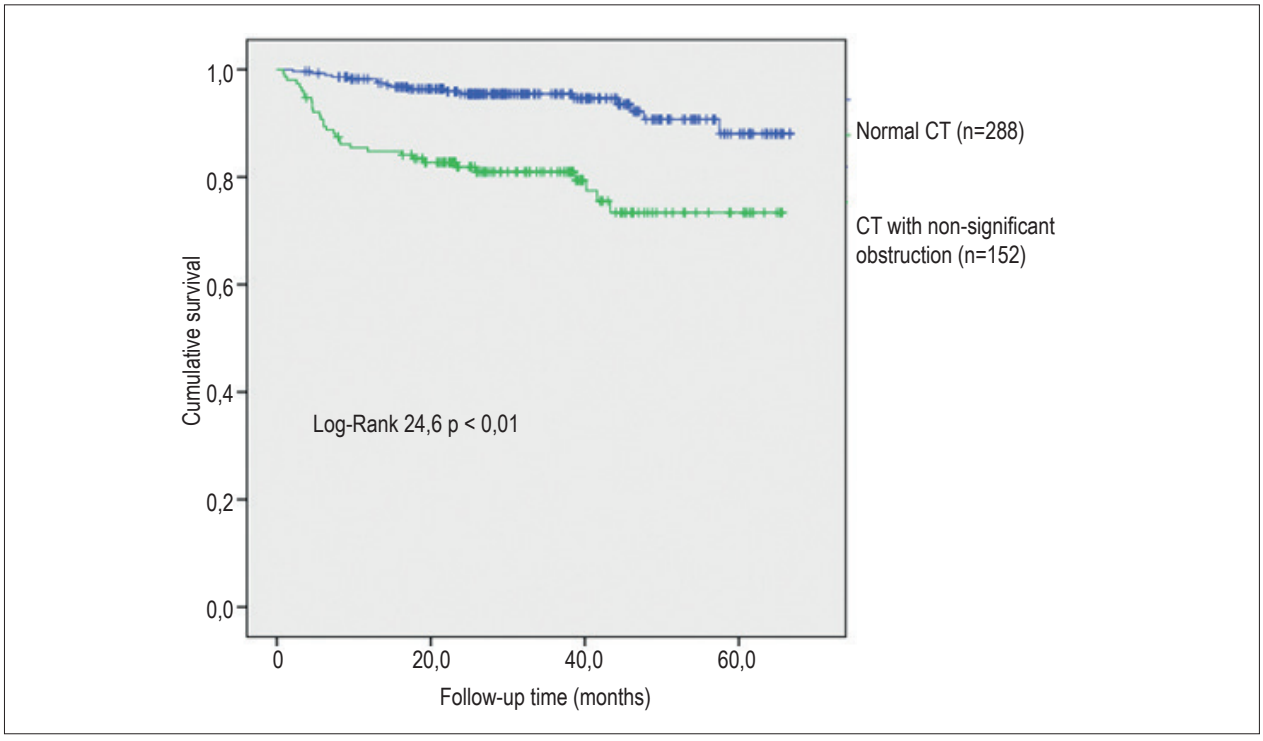

Figure 1 – *Event-free survival in patients with normal MDCT and non-significant obstruction on MDCT.*

Discussion

Our study provides evidence that atherosclerotic obstruction clinically insignificant on CT is an independent predictor of future cardiac events and has incremental value in predicting coronary events compared to conventional risk factors. Other independent risk factors for coronary events highlighted in our study were age and the presence of hypertension.

Obstructive coronary events result from the interaction between thrombosis and vasospasm on atherosclerotic lesions in the coronary arteries, and may present various clinical conditions such as unstable angina, acute myocardial infarction, need for coronary artery bypass grafting or sudden death. In principle, only the atherosclerotic plaques with clinically significant obstruction restricting the lumen of the vessel by more than 50% were considered to have potential for rupture, subsequent thrombosis and vascular occlusion. Later studies showed that even plaques without significant obstructive lesions, i.e., narrowing of the vascular lumen smaller than 50%, also have thrombogenic potential associated with high risk of mortality[2-3]. By focusing on severe coronary stenosis, we limited our study to only one of the variables of atherosclerotic plaque that determine coronary resistance, neglecting relevant aspects such as length, shape and eccentricity, and the presence of stenosis in series, severely affecting blood flow[9]. On the other hand, coronary atherosclerosis can be present even in angiographically normal arteries because of external remodeling in the presence of atherosclerotic plaques that do not lead to a significant intraluminal stenosis[4,10]. As noted, these "hidden" lesions can be asymptomatic for many years until they cause thrombosis, since they do not produce stress-induced ischemia. The rupture of non-stenotic vulnerable plaques can cause fatal cardiac events and the detection of these plaques may allow for optimal risk stratification before a severe CAD result. New advances of CT led to the ability to identify and directly quantify these "vulnerable" plaques, which have positive remodeling characteristics and low-density components[9].

Since the introduction of CT, studies have been published comparing the diagnostic performance of this method with the reference standard, invasive coronary angiography. The high diagnostic accuracy (around 90%) for detection and exclusion of coronary stenosis on CT has been established[7,8,11]. Although the association between ACS and not clinically significant atherosclerotic obstruction has been described since the 1970s[12], there is still no definition in the literature about the prognosis and risk factors, as well as on the predictive capacity of coronary adverse events on CT for this group of patients[8,13,14]. It is known that individuals undergoing CT commonly present clinically non-obstructive plaques and these may prove to be involved in the pathophysiological process of acute coronary insufficiency[9,15-17]. Furthermore, plaques with no clinically significant obstruction may be most frequently associated with adverse events for being more frequent than plaques with significant obstruction[4,5,18]. Patients with obstruction < 50% on CT may be at higher risk for morbidity and mortality, as demonstrated in our study. Nevertheless, they represent a patient population, in which the functional tests commonly used in the evaluation of coronary artery disease (exercise testing, myocardial scintigraphy and stress echocardiography) may prove negative, because these lesions do not determine exercise-induced myocardial ischemia, not allowing diagnosis of not hemodynamically significant arteriosclerotic lesions[19].

Among the limitations of our study, we can mention the restriction of the study to a single center as well as a wide range of different conditions associated with the indication of the test. The MDCT results have the potential to influence the decision of CABG indication and may change the outcome in this study. However, we consider as an adverse event only those that occurred after three months of follow-up (average 33 months, ranging from 3 to 67 months). After this period, the CABG indication was based on clinical decision as per established guidelines. However, the CT result may be a confounding factor, being associated with the CABG outcome. Although the study population was small, it met the required size of the sample calculation, which allows the study to serve as a hypothesis generator for other studies of greater impact. The use of combined outcomes, such as that used in our study, has been widely used in various studies and has advantages such as increased study power and disadvantages, such as the heterogeneity of the importance and frequency of each outcome assessed[20].

Conclusion

The presence of non-significant atherosclerotic obstruction (<50% of the coronary lumen) demonstrated by CT in patients with suspected CAD proved to be an independent predictor of clinical events compared to conventional risk factors and may be useful in the risk stratification of these patients.

Authors' Contribution

Research creation and design: Barros MVL; Data acquisition: Barros MVL, Siqueira BP, Guimaraes CCB, Cruz DFS,Guimaraes LAA, Lima MMP, Siqueira MHA; Data analysis and interpretation: Barros MVL, Nunes MCP, Siqueira BP, Guimaraes CCB, Cruz DFS, Guimaraes LAA, Lima MMP, Siqueira MHA; Statistical analysis: Barros MVL,Nunes MCP; Manuscript drafting: Barros MVL,Siqueira BP, Guimaraes CCB, Cruz DFS, Guimaraes LAA, Lima MMP, Siqueira MHA; Critical review as for important intellectual content: Barros MVL,Nunes MCP.

Potential Conflicts of Interests

No potentially relevant conflicts of interests.

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Academic Association

This study is not associated to any graduate programs.

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