Cardiac catheterization with normal coronary arteries: prevalence rate and analysis of predictor variables

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ABSTRACT – Objective: To assess the percentage of patients with normal coronary angiography in a hospital and to determine the predictor variables of this finding. Methods: All elective coronary angiographies performed from April to October 2018 were analyzed, excluding patients with valve diseases and who had a previous catheterization. A total of 503 patients were recruited, divided into 2 groups: Group A for normal coronary arteries, and group B for coronary artery disease. Coronary vessels with diameter ≥2.0mm and with no stenosis ≥40% determined by quantitative coronary angiography were considered normal. After the univariate analysis of the differences between groups, a multivariate analysis was performed by logistic regression, to determine the independent predictors of a normal exam. Results: The clinical characteristics were as follows: mean age of 62 years; 55% male; hypertension present in 86%; diabetes mellitus in 35%; smoking habit reported by 20.5%; dyslipidemia present in 20.5%; and family history of coronary artery disease in 59%. The prevalence of normal coronary angiography was 45%. In the univariate analysis, there were differences between the two groups in regard to sex, age, symptoms, diabetes mellitus and smoking habit. In the multivariate analysis, female sex (OR=3.22; 95%CI 2.20-4.80; p<0.0001), younger age (OR=0.96; 95%CI 0.94-0.98; p<0.0001), absence of diabetes mellitus (OR=0.46; 95%CI 0.30-0.70; p<0.0001), and no smoking habit (OR=0.33; 95%CI 0.19-0.55; p<0.0001) were predictors of normal coronary angiography. Conclusion: The prevalence of normal coronary arteries in this study was high. Female sex, younger age, absence of diabetes mellitus, and no smoking habit were independent predictors of this finding.

Keywords: Cardiac catheterization; Coronary artery disease; Coronary vessels

RESUMO – Objetivo: Averiguar o percentual de pacientes com coronariografia normal em um hospital e determinar as variáveis preditoras desse achado. Métodos: Foram analisadas todas as coronariografias eletivas realizadas de abril a outubro de 2018, excluindo pacientes com doenças valvares que já tinham cateterismo prévio. Foram recrutadas 503 pacientes, divididos em 2 grupos: A para coronárias normais e B para doença arterial coronariana. Foram consideradas coronárias normais vasos ≥2,0mm e sem lesões ≥40% pela angiografia coronariana quantitativa. Após análise univariada das diferenças entre os grupos, foi realizada análise multivariada por regressão logística, para determinar os preditores independentes de um exame normal. Resultados: As características clínicas foram as seguintes: média de idade de 62 anos; 55% do sexo masculino; hipertensão arterial sistêmica presente em 86%; diabetes melito em 35%; tabagismo relatado por 20,5%; dislipidemia encontrada em 20,5%; e achado de história familiar de doença arterial coronariana em 59%. A prevalência de coronariografia normal foi de 45%. Na análise univariada, houve diferença entre os dois grupos em relação a sexo, idade, sintomas, diabetes e tabagismo. Na análise multivariada, sexo feminino (RC=3,22; IC95% 2,20-4,80; p<0,0001), idade mais jovem (RC=0,96; IC95% 0,94-0,98; p<0,0001), ausência de diabetes melito (RC=0,46; IC95% 0,30-0,70; p<0,0001) e não tabagistas (RC=0,33; IC95% 0,19-0,55; p<0,0001) foram preditores de coronariografia normal. Conclusões: A prevalência de coronárias normais neste estudo foi elevada. Sexo feminino, idade mais jovem, ausência de diabetes melito e não tabagistas foram preditores independentes desse achado.

Descritores: Cateterismo cardíaco; Doença da artéria coronariana; Vasos coronários
INTRODUCTION

Cardiac catheterization, or cineangiocoronangiography, is the gold standard method for defining coronary anatomy. It is an invasive exam, with low rates of complications, according to the literature.\(^1\)\(^2\) Data from the Society for Cardiac Angiography and Interventions (SCAI) registry show that the mortality rate of cardiac catheterization is very low, around 0.11%, and this finding was corroborated in two national publications, of 1991 and 2007.\(^2\)\(^3\)

Information obtained from the website of the Information Technology Department of the Brazilian Public Health System (DATASUS; http://www2.datasus.gov.br/DATASUS/) shows that the number of catheterizations performed in the country increased over 500% between 2000 and 2010, and this number has remained stable over the past 7 years. In 2017, a total of 123,576 outpatient catheterizations were performed in our country by the Brazilian Public Health System (SUS), with more than 50% of these procedures occurring in the Southeast Region. This implies an increase in health care costs (both public and private), inasmuch as catheterization is considered a high cost, albeit outpatient, procedure. In addition, despite being safe, it is nonetheless an invasive examination, and a complex hospital structure is required to conduct it.

Several studies have been published in recent years to analyze the prevalence rates of normal coronary angiography and investigate the possible causes thereof. These studies involved hundreds of thousands of patients in the United States and Europe, and showed normal test result rates ranging from 20% to 70%, depending on the location where the test was performed, and on characteristics of the patients.\(^4\)\(^5\) In Brazil, we do not yet have a large or even medium-sized study that has analyzed the rate of elective outpatient catheterizations, with normal coronary arteries.

The objective of the present study is to determine the percentage of patients who underwent cardiac catheterization and had normal coronary arteries among those referred for elective catheterization, in addition to correlating these findings with the clinical characteristics of the patients and the ancillary tests performed on them, with the purpose of finding possible explanations for these data.

METHODS

We prospectively evaluated all patients referred for elective cardiac catheterization in a private hospital in Cabo Frio (RJ), which is a SUS reference center for high complexity in cardiology in the State of Rio de Janeiro, from April to November 2018 (7 consecutive months), excluding patients with known coronary artery disease, who had only heart valve disease, under 18 years of age, and pregnant. Among the recruited patients, 448 (89%) came from SUS, and 55 (11%) from many different health care plans.

The patients had a previous interview with a nurse, who filled out a questionnaire designed to collect all information relevant to the case. This questionnaire also included the final result of the test, filled in by the physician.

After examination, the patients were divided into two groups: Group A, catheterization with normal coronary arteries; and Group B, patients with significant coronary artery disease (CAD).

All catheterizations showing coronary vessels with diameter ≥2.0mm and with no stenosis ≥40% determined by quantitative coronary angiography (QCA) were considered normal. We decided to use 40%, not 50%, because the measurement was not performed by angiographic visual estimation, but by a computerized analysis of the lesion (QCA), which is known to produce significant differences in its quantification.\(^7\)\(^9\)

Statistical analysis

All variables were tested for normality by the Shapiro-Wilks and/or Kolmogorov-Smirnov tests. In the descriptive analysis, the numerical variables were presented as mean±standard deviation (SD) or medians and inter-quartile ranges, and the categorical variables as n (%). The Chi-squared test and the Fisher’s exact test were used to compare categorical variables; the unpaired Student’s \(t\) test and the Wilcox-Mann-Whitney test were used for continuous variables.

After univariate analysis, variables whose differences between groups were significant (\(p<0.05\)) were subjected to multivariate analysis by logistic regression, to determine the independent predictors associated with normal coronary angiography and the respective odds ratios (OR). We used the Wald test to determine the significance of the regression coefficients. To assess the goodness of fit of the statistical model, the Deviance test and the Pearson’s Chi-squared test were used. Statistical analysis was performed using the R 3.6.1 (R Core Team, Vienna, Austria) software. Values of \(p<0.05\) were considered statistically significant, and all tests were two-tailed.

This study was evaluated and approved by the Research Ethics Committee of the Escola de Medicina Souza Marques da Fundação Técnico-Educativo Souza Marques (protocol 3.772.532, CAAE 25803319.3.0000.5239).

RESULTS

During a period of seven consecutive months, 743 patients were admitted to our service to undergo some type of interventional cardiology procedure. Of these, 167 underwent angioplasty with or without stenting, 22 were previously revascularized patients undergoing reassessment, 9 had valve diseases, and 42 had been previously examined and had coronary artery disease, and were excluded from the study. Thus, 503 patients were included in the study.
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Figure 1. Overview of the study protocol and group formation.

Group A: catheterization with normal coronary arteries; Group B: significant coronary artery disease.

CAT: coronary angiography; CAD: coronary artery disease.

Figure 2. Normal coronary angiographies in the studied population.

The clinical characteristics of these patients can be analyzed in Table 1. Most patients (55%) were male, mean age of 63 years. About 74% had stable angina or silent ischemia. We draw attention to the prevalence of hypertension (86%), family history of CAD (59%), and diabetes mellitus (35%) in the studied population.

Table 1. Clinical characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n=503)</th>
<th>CAD (n=277; 55%)</th>
<th>Normal CAT (n=226; 45%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63 (55-69)</td>
<td>65 (57-71)</td>
<td>61 (53-67.7)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Female</td>
<td>44.9</td>
<td>33.6</td>
<td>58.8</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>White race</td>
<td>71.2</td>
<td>72.6</td>
<td>69.5</td>
<td>0.49</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical angina</td>
<td>204 (40.6)</td>
<td>108 (39.0)</td>
<td>96 (42.5)</td>
<td></td>
</tr>
<tr>
<td>Atypical pain</td>
<td>130 (25.8)</td>
<td>60 (21.7)</td>
<td>70 (31.0)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>169 (33.6)</td>
<td>109 (39.4)</td>
<td>60 (26.5)</td>
<td></td>
</tr>
<tr>
<td>Prior NIT</td>
<td>149 (29.6)</td>
<td>73 (26.4)</td>
<td>76 (33.6)</td>
<td>0.078</td>
</tr>
<tr>
<td>NIT positive†</td>
<td>100 (67.1)</td>
<td>53 (72.6)</td>
<td>47 (61.8)</td>
<td></td>
</tr>
<tr>
<td>NIT negative†</td>
<td>49 (32.9)</td>
<td>20 (27.3)</td>
<td>29 (38.2)</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>433 (86.1)</td>
<td>233 (84.1)</td>
<td>200 (88.5)</td>
<td>0.195</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>299 (59.4)</td>
<td>159 (57.4)</td>
<td>140 (61.9)</td>
<td>0.316</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>177 (35.2)</td>
<td>114 (42.2)</td>
<td>63 (27.9)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>103 (20.5)</td>
<td>60 (21.7)</td>
<td>43 (19.0)</td>
<td>0.51</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>103 (20.5)</td>
<td>70 (25.3)</td>
<td>33 (14.6)</td>
<td>0.0038*</td>
</tr>
<tr>
<td>PVD</td>
<td>40 (8.0)</td>
<td>27 (9.7)</td>
<td>13 (5.8)</td>
<td>0.135</td>
</tr>
<tr>
<td>Stroke</td>
<td>38 (7.6)</td>
<td>22 (7.9)</td>
<td>16 (7.1)</td>
<td>0.738</td>
</tr>
<tr>
<td>COPD</td>
<td>25 (5.0)</td>
<td>10 (3.6)</td>
<td>15 (6.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>CRF</td>
<td>10 (2.0)</td>
<td>5 (1.8)</td>
<td>5 (2.2)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Results expressed as median (percentiles), % or n (%).

* Significant; † for ischemia. The percentages of NIT positive and negative results were calculated in relation to the total population undergoing the procedure (149 patients, 73 in the CAD group, and 76 in the normal CAT group).

CAD: coronary artery disease; CAT: coronary angiography; NIT: non-invasive test; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure.

A total of 149 (30%) non-invasive tests (NIT) were performed on patients referred for the study (106 treadmill tests, and 43 scintigraphies). Of these, 100 (67%) presented a positive test for ischemia. However, after catheterization, only 53% of patients with positive tests for ischemia showed significant CAD on angiography.

In the univariate analysis, there were statistically significant differences between Groups A and B in regard to the variables age, sex, symptoms, diabetes mellitus, and smoking habit. Inserting these variables in the statistical model of multivariate analysis by logistic regression, we found that female sex implied a three-fold greater possibility of a normal test (OR=3.22; 95%CI 2.17-4.83; p<0.0001) (Table 2 and Figure 3). The variable age was also a predictive factor for normal coronary angiography (the younger the age, the greater the chance of a normal exam), as well as the absence of diabetes mellitus and smoking habit. Smokers had a 67% lower chance of having a normal test result when compared to non-smokers (OR=0.33; 95%CI 0.19-0.55; p<0.0001), and diabetic patients had a 54% lower chance of a normal catheterization when compared to non-diabetic patients (OR=0.46; 95%CI 0.30-0.70; p<0.0001) (Table 2 and Figure 3).
DISCUSSION

The present study showed a 45% rate of normal coronary angiographies in a private hospital in the city of Cabo Frio. In the multivariate analysis by logistic regression, the only variable that remained as a predictor of normal coronary angiography was female sex (OR=3.22; 95%CI 2.17-4.83; p<0.0001). Absence of diabetes mellitus and smoking habit, and less advanced age were also associated with a higher rate of normal coronary angiography.

This finding is of great importance, since it raises fundamental questions, many of which are still unanswered and may have a major impact on the public health system in Brazil: are we actually ordering too many unnecessary tests? What are the minimum criteria to be used to refer a patient to coronary angiography? Ischemia is sometimes detected in a coronary angiography test considered normal. What is the clinical and prognostic significance of this? Some of these questions have been the subject of studies in recent years, but still have no definitive answers.

Several studies carried out internationally have shown prevalence rates of normal coronary angiography between 20% and 70%, depending on the location where the test was performed and the clinical characteristics of the patients. The study by Douglas et al. involved 565,504 elective patients in the period from 2005 to 2008, and used any lesion ≥50% in large vessels, by visual estimation, as a criterion for the diagnosis of CAD, presenting a disease rate of only 45% (39% to 52%). These findings are in line with our study, drawing attention to the fact that our criterion for defining CAD was a lesion ≥40% by QCA, which expands the spectrum of vessels that are considered diseased, although it is known that the visual estimation can overestimate lesions in 20% of cases.

A study conducted by Bradley et al. involved 22,538 patients referred for elective catheterization between 2007 and 2010 and showed a normal test result rate (the criterion used was injury <20% by visual estimation) of 21.4%. Patients with an important family history of CAD and with indicators for emergency coronary angiography were excluded from this study. Patients with normal coronary angiography were younger, and had a higher rate of female and non-white individuals. The low rate of normal test results in this study can be attributed to its criteria for normal test result (lesion <20%). This study also used another definition, non-obstructive CAD (lesions ≥20% and <50%), and 41% to 56% of cases were included into this classification - the rates varied according to the hospital where the cases were recruited. These findings are also in agreement with those of our study, as well as the factors associated with normal coronary angiography or non-obstructive CAD, such as, for example, younger age and female sex.

The study by Patel et al. carried out in 663 American hospitals, showed only 37.6% of patients with CAD out of a total of 398,978 patients recruited in the study. The criteria used for the diagnosis of CAD were lesions >50% in the left main coronary artery or >70% in a main vessel or branch >2.0mm in diameter, by visual estimation. Although these criteria are apparently more stringent, this study still showed that 39.2% of cases had entirely normal coronary arteries (lesions <20%). The predictor variables of an altered test result were male sex, advanced age, diabetes mellitus and dyslipidemia - widely known risk factors for CAD. Once again, the results are in agreement with our study.

An important data of this study concerns the number of patients undergoing NIT before coronary angiography, which was 84%, compared to only 30% in our study. However, the criteria used in the Patel et al. study to define NIT

### Table 2. Odds ratio for normal coronary angiography with a 95% confidence interval

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.96</td>
<td>0.94-0.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>3.22*</td>
<td>2.17-4.83</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Symptoms</td>
<td>0.76</td>
<td>0.48-1.20</td>
<td>0.25</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>0.33</td>
<td>0.19-0.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.46</td>
<td>0.30-0.70</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Significant.

OR: odds ratio; CAT: coronary angiography.

**Figure 3.** Forest plot graph of predictor variables for cardiac catheterization with normal coronary angiography using the multivariate analysis model by logistic regression. The variable most associated with the possibility of a normal test (to the right of the graph) is female sex. On the other hand, age (advanced), diabetes mellitus, and smoking habit (the last three to the left of the midline) decrease the probability of a normal test (odds ratio <1).
were very broad, including resting electrocardiogram, coronary computed tomography angiography, and stress tests. In our study, only ischemia-inducing tests were considered non-invasive, such as stress tests, scintigraphy, and stress echocardiography. Our sample is in agreement with the American health system (Medicare) database, which points out that only 44.5% of this population underwent some ischemia-inducing test before coronary angiography. Furthermore, even conducting a prior NIT does not ensure that the catheterization will be altered, as shown by some studies, given the low positive predictive value of these tests in populations with a low pretest probability of having coronary heart disease, which was exactly the finding of our study (only 53% of patients with NIT positive for ischemia had CAD).

In our study, it was not surprising to find that female sex is a predictor of normal coronary angiography. It is known that the prevalence of CAD in women is lower than in men, and NIT tends to yield more false-positive results in female patients (due to low pretest probability of CAD and greater frequency of atypical symptoms). In our series, of 47 patients with NIT false-positive results, 62% were female, and 55% of these had atypical pain.

Our study also confirmed a well-known conclusion: older age, diabetes mellitus and smoking habit are associated with a greater incidence of CAD. On the other hand, younger patients, absence of diabetes mellitus, and absence of smoking habit are associated with a significantly greater chance of normal coronary angiography, a finding in our study that confirms data previously published by Bradley et al. and Patel et al.

This study has some limitations. It is the experience of a single center, which is a reference in high complexity cardiology in SUS, and therefore may not reflect the reality of other hospitals, as shown in the study by Bradley et al. The patients were referred from different municipalities. Some of them had a previous cardiologist, and others had their exams ordered by general practitioners, rendering difficult the analysis of the referral criteria for coronary angiography. In any case, this reflects the reality in our country, where it is common for patients in the public system to seek treatment only in emergencies, in the face of chest pain or dyspnea, which is often not due to CAD, being referred to coronary angiography without adequate stratification. Finally, most of the patients in our sample did not undergo ischemia-inducing NIT before coronary angiography, and this may contribute to higher rates of normal exams, despite being in accordance with the latest reports in the literature. We believe that this is due to the fact that the majority of our patients came from SUS (89%), which makes it even more difficult to perform NIT before coronary angiography. For this reason, our study may not reflect the reality of the private health system in Brazil, in which adequate stratification before coronary angiography is more frequent.

CONCLUSION

In the population studied, the rate of normal coronary angiographies, defined as the absence of a lesion with a diameter stenosis ≥40% in main coronary vessels or branches ≥2.0mm in diameter, was 45%, and the predictor variables of normal examination were female, younger age, absence of diabetes and non-smokers.

This finding raises important questions for the public health system in Brazil and requires larger, multicenter studies, involving a large number of patients, to confirm the results and define new guidelines - perhaps more rigorous - for ordering invasive tests, such as cardiac catheterization.

SOURCE OF FINANCING

None.

DECLARATION OF CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: LBS, FMS and SLMC; data collection: LBS, FMS and SLMC; data interpretation: LBS, FMS and MAP; writing of the text: LBS and FMS; approval of the final version to be published: LBS, FMS, SLMC and MAP.

REFERENCES


