

Predictors of Angiographically Normal Coronary Arteries in Stable Patients with Suspected Coronary Disease.

Predictores de Arterias Coronarias Angiográficamente Normales en Pacientes Estables con Sospecha de Enfermedad Coronaria

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ABSTRACT

Introduction: Coronary angiography (CA) is the gold standard test to identify patients with coronary artery disease. Despite a proportion of normal CA is expected, this study should be minimized, given its invasive nature, the associated risk and increased health costs.

Objectives: The aim of this study was to establish the characteristics, epidemiological patterns and variables associated to angiographically “normal” coronary arteries in stable patients referred for CA.

Methods: Coronary angiographies were analyzed in 12,686 patients from five centers in Buenos Aires. All data were retrospectively obtained from 2008 to 2013. Coronary angiographies with < 50% lesions were defined as “normal”. Demographic characteristics, usual risk factors, chronic renal failure, hypothyroidism, peripheral vascular disease, symptoms, ischemia-inducing tests and social coverage were compared between the group with “normal” CA and patients with ≥ 50% obstructive coronary disease.

Results: Among the 3,990 patients included in the study (31.5%), 38.6% had a normal CA, and female gender was the most important independent predictor for this finding. In addition, younger age and absence of ischemic symptoms were associated with greater probability of “normal” CA.

Conclusions: In a population referred for CA diagnosed with stable coronary artery disease, female gender, younger age and absence of symptoms were associated with angiographically “normal” coronary arteries. Better use of clinical stratification models could optimize CA performance to detect patients with significant coronary artery disease, limiting unnecessary studies.

Key words: Predictors - Stable Coronary Artery Disease - Normal Coronary Arteries - Coronary Angiography - Female Gender.

RESUMEN

Introducción: La cinecoronariografía (CCG) es la prueba que se constituye en el estándar de oro para identificar a pacientes con coronariopatía. Pese a que se prevé una proporción de CCG normales, este estudio debe minimizarse, dados su carácter invasivo, el riesgo asociado y el aumento del costo en salud.

Objetivos: Determinar las características, los patrones epidemiológicos y las variables relacionadas con el hallazgo de arterias coronarias angiográficamente “normales” en pacientes estables derivados para la realización de una CCG.

Material y métodos: Se analizaron las CCG de 12.686 pacientes de cinco centros de Buenos Aires. Todos los datos se obtuvieron en forma retrospectiva entre 2008 y 2013. Se definió “normal” a una CCG con lesiones <50%. Se compararon las características demográficas, los factores de riesgo habituales, la presencia de insuficiencia renal crónica, de hipotiroidismo y de enfermedad vascular periférica, los síntomas, los estudios evocadores de isquemia y la cobertura social entre el grupo con CCG “normal” y los pacientes con coronariopatía obstructiva ≥ 50%.

Resultados: De los 3.990 pacientes incluidos (31,5%), el 38,6% presentaba una CCG normal. El sexo femenino fue el mayor predictor independiente para este hallazgo. Además, la menor edad y la ausencia de síntomas compatibles con isquemia se asociaron con una probabilidad mayor de una CCG “normal”.

Conclusiones: En una población derivada para CCG con diagnóstico de enfermedad arterial coronaria estable, el género femenino, la menor edad y la ausencia de síntomas se relacionaron con el hallazgo de arterias coronarias angiográficamente “normales”.

Un mejor uso de los modelos de estratificación clínica podría optimizar el rendimiento de la CCG para detectar pacientes con enfermedad arterial coronaria significativa, limitando así los estudios innecesarios.

Palabras clave: Predictores - Enfermedad coronaria estable - Coronarias normales - Cinecoronariografía - Sexo femenino

REV ARGENT CARDIOL 2015;83:25-30. <http://dx.doi.org/10.7775/rac.v83.i1.4856>

SEE RELATED ARTICLE: Rev Argent Cardiol 2015;83:3-4. <http://dx.doi.org/10.7775/rac.v83.i1.5720>

Received: 07/31/2014 Accepted: 10/22/2014

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Abbreviations

CA	Coronary angiography
CAD	Coronary artery disease

CRF	Chronic renal failure
ACS	Acute coronary syndrome

INTRODUCTION

Coronary angiography (CA) plays a key role in the diagnosis and management of patients with coronary artery disease (CAD), constituting the gold standard to identify these patients. However, it is associated with a small risk of severe complications, estimated in less than 1%, and vascular complications of around 2% to 4%. (1, 2)

Previous studies have demonstrated the importance of implementing an effective strategy to adequately determine the probability of significant CAD development by risk groups. As a result CA diagnostic performance could be optimized. (3) Although it is known that a proportion of CA will be normal, it is important to minimize this finding in order to reduce the number of studies indicated in patients without disease, given the invasive character of angiography, its risk and the associated increase in health costs. (4-6)

In stable individuals who undergo an evaluation to determine the presence of obstructive coronary disease, diagnosis and treatment guidelines recommend clinical observation when they are defined as low risk, the use of ischemia-inducing tests to evaluate the need for CA in moderate risk and indication of CA at high risk. (6,7)

The aim of this study was to determine the characteristics, epidemiological patterns and variables related to angiographically "normal" coronary arteries in a population of consecutive, clinically stable patients referred for CA due to symptom presentation or complementary studies compatible with the presence of significant CAD.

METHODS

Between January 2008 and December 2013, 12,686 patients with suspected significant CAD consecutively underwent CA in the hemodynamics laboratory of five centers of Buenos Aires. All data were obtained retrospectively from a database (Microsoft Access, Microsoft™) developed for the collection and analysis of patient characteristics and to make a report of CA results.

The studies were performed by femoral or radial artery access according to the usual technique. (8)

Stenosis was visually estimated by the interventional cardiologist. Coronary arteries presenting angiographic lesions < 50% in any major epicardial artery (anterior descending, circumflex and/or right coronary artery) or second order arteries > 2 mm in diameter were defined as angiographically "normal". Angiographically significant CAD was established when there was evidence of epicardial stenosis ≥ 70% in the anterior descending, circumflex and right coronary arteries, or ≥ 50% in the left main coronary artery.

Existing lesions presenting between 50% to 69% luminal obstruction were considered as moderate.

Two groups were compared: those with lesions < 50%

(angiographically "normal" coronary arteries) and those with lesions ≥ 50% ("pathological" coronary arteries). The latter group included patients with lesions defined as moderate or significant, since few cases were classified in this way.

Inclusion criteria:

- Patients > 18 years referred for CA study.
- Suspected stable CAD defined by typical anginal symptoms and/or positive ischemia-inducing tests.

Exclusion criteria:

- Present acute coronary syndrome.
- Hemodynamic instability.
- History of CAD (myocardial infarction, percutaneous coronary intervention or prior coronary artery bypass graft surgery).
- Patients referred for CA due to other reasons (e.g. valve disease in surgical plan) that were asymptomatic and/or without evidence of test-induced ischemia.

Ischemia-inducing tests

Graded exercise testing, gamma camera with CT slices and exercise or pharmacological stress echocardiography were considered ischemia-inducing tests. The results were documented as positive or negative. The available stress test results were compared with the proportion of normal CA.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies. Continuous and categorical variables were compared using Student's t test or the chi-square test, as appropriate. The initial statistical analysis included comparison of demographic data, conventional risk factors, chronic renal failure (CRF), hypothyroidism, peripheral vascular disease, health insurance and performing center. Chronic renal failure was defined as an estimated creatinine clearance < 50 ml/min.

Univariate and multivariate logistic regression models were used to estimate the predictors of an angiographically "normal" coronary artery. The odds ratio (OR) and the 95% confidence interval (CI) were calculated in these models.

A multivariate logistic regression analysis (backward stepwise method) was performed to determine which factors were associated with the endpoint. The variables associated with events in the univariate analysis with $p < 0.10$ entered the model. A p value < 0.05 was considered as statistically significant. The EpiInfo™ 7.1.0.6 software package was used for data analysis.

Ethics considerations

The protocol was reviewed and approved by the Ethical Board of each institution, excluding the informed consent form as no sensitive data or clinical follow-up were required (in accordance to the Habeas Data Act 23,326 on Protection of Personal Data).

RESULTS

From the total number of patients undergoing CA (n

= 12,686), 8,696 were excluded. Among these, 5,934 (46.8%) presented ACS or hemodynamic instability, 1,756 (13.8%) had known CAD and 1,006 (7.9%) had no symptoms or studies compatible with myocardial ischemia. The study included 3,990 patients (31.5%) for data analysis (Figure 1).

In the study sample most patients were men (65.2%) and mean age was 63.4 ± 11 years. The most prevalent risk factor was hypertension (79.5%), followed by dyslipidemia (42%), diabetes (18.1%), obesity (17.7%) and smoking (12.5%). The prevalence of other cardiovascular diseases such as stroke, peripheral vascular disease and heart failure was low (0.8%, 1.5% and 0.5%, respectively). Most patients (92.8%) had health insurance coverage (60.5% private health insurance and 32.3% PAMI). Of all the patients included in the study, 90.4% reported symptoms attributable to coronary heart disease, while 71.2% had undergone an ischemia-inducing test, which was positive in 96.2% of cases.

Patients had a normal CA in 38.6% of cases, varying from 34.4% to 43.8% among different centers. Moderate lesions as single diagnosis were observed in 194 patients (7.9%). In the univariate analysis, patients presenting with angiographically normal coronary arteries compared to pathological CA were mostly women (48% vs. 23.9%) and were significantly younger. In this group there was a lower prevalence of all traditional risk factors and CRF, but hypothyroidism was more frequent (3.0% vs. 1.2%). Absence of symptoms or a positive ischemia-inducing test was also predictor of normal CA (Table 1).

In the multivariate analysis, female gender was the strongest independent predictor of normal CA (OR: 4.2; 95% CI 3.62-4.95), as were younger age and absence of symptoms consistent with ischemia. Both

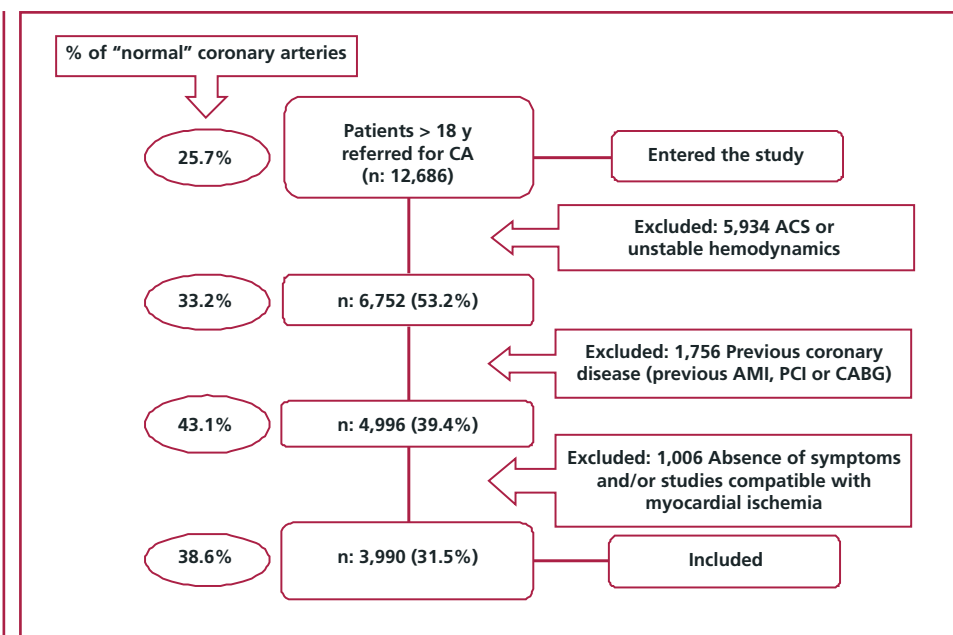
hypothyroidism and absence of a positive ischemia-inducing test were associated with a higher probability of “normal” CA, although in neither case this finding was statistically significant (p = 0.06). Traditional risk factors, excluding hypertension, were inversely associated with “normal” CA. (Table 2).

DISCUSSION

About 40% of stable patients with symptoms and/or ischemia-inducing tests suggestive of CAD submitted to a diagnostic CA presented angiographically “normal” arteries.

Although several similar previously published studies postulate that the frequency of “normal” CA could be used as an indicator of the potential performance of the method, their results have important limitations. (9) In 1992, the RAND Corporation reported that between 9% and 36 % of patients who underwent CA had normal coronary arteries. In this study there were different definitions of “normal” and several variations in the radiographic systems used. (10) The CASS study, with 21,487 CA analyzed, showed that 18.8% of patients had a “normal” study, defined as the absence of stenosis ≥ 50% in all major epicardial vessels. (11) A more recent study by The Society for Cardiac Angiography and Interventions Registry (SCAI) revealed that 20% to 27% of patients had “normal” coronary arteries and that 30% to 35% of them had less than 50% stenosis in all vessels. (12, 13) These data, obtained from more than 200,000 patients in the course of several years, cover a wide spectrum of individuals who were referred for CA, such as those admitted for acute myocardial infarction and other emergencies or urgent indications. Therefore, the definition of study population characteristics is critical for the analysis of results.

Fig. 1. Study population and exclusion criteria. y: Years. CA: Coronary angiography. ACS: Acute coronary syndrome. AMI: Acute myocardial infarction. PCI: Percutaneous coronary intervention. CABG: Coronary artery by-pass graft surgery.



	Total n=3,990 (31,5%)	Coronary arteries with lesions < 50% n=1,539 (38,6%)	Coronary arteries with lesions ≥ 50% n=2,451 (61,4%)	p
Age	(mean ± SD)	(mean ± SD)	(mean ± SD)	
	63.4±11	60.4±11	63.9±11.9	<0.001
Gender	n (%)	n (%)	n (%)	
Female	1,387 (34.8%)	739 (48%)	587 (23.,9%)	<0.001
Cardiovascular risk factors				
HT	3,171 (79.5%)	1,163 (75.6%)	2,008 (81.9%)	<0.001
DLP	2,316 (42.0%)	492 (32.0%)	1,182 (48.2%)	<0.001
DM	720 (18.1%)	187 (12.2%)	533 (21.7%)	<0.001
S	497 (12.5%)	156 (10.1%)	341 (13.9%)	<0.001
Obesity	708 (17.7%)	324 (21.1%)	384 (15.7%)	<0.001
Cardiovascular history				
LL vascular disease	61 (1.5%)	19 (1.2%)	42 (1.7%)	ns
HF	20 (0.5%)	8 (0.5%)	12 (0.5%)	ns
Stroke	31 (0.8%)	11 (0.7%)	20 (0.8%)	ns
PVD	91 (2.3%)	29 (1.9%)	62 (2.5%)	ns
Other medical conditions				
CRF	125 (3.1%)	30 (1.9%)	95 (3.9%)	<0.001
Hypothyroidism	75 (1.9%)	46 (3.0%)	29 (1.2%)	<0.001
Angina or equivalent conditions	3,606 (90.4%)	1,367 (88.8%)	2,239 (91.4%)	0.01
Ischemic test (+)	2,732 (68.5%)	1,014 (65.9%)	1,718 (70.1%)	0.006
Silent ischemia	234 (5.9%)	102 (6.6%)	132 (5.4%)	ns
Health insurance				
Without HI	291 (7.3%)	114 (7.4%)	177 (7.2%)	ns
Private HI	2412 (60.5%)	1017 (66.1%)	1395 (56.9%)	p<0.001
PAMI	1287 (32.2%)	408 (26.5%)	879 (35.9%)	p<0.001

SD: Standard deviation. HT: Hypertension. DLP: Dyslipidemia. DM: Diabetes mellitus. S: Smoking. CRF: Chronic renal failure. LL: Lower limbs. HF: Heart failure. PVD: Periferal vascular disease. HI: Health insurance. PAMI: Integral Medical Assistance Program. ns: Not significant.

Table 1. Baseline characteristics and univariate analysis according to the presence or absence of "normal" CA.

Table 2. Multivariate model to predict "normal" CA based on the characteristics of the included cohort.

	OR	95% CI		p
Age	0.95	0.94	0.96	<0.001
Women	4.21	3.60	4.92	<0.001
HT	0.90	0.75	1.07	ns
DLP	0.50	0.43	0.59	<0.001
DM	0.50	0.41	0.61	<0.001
S	0.46	0.37	0.58	<0.001
Obesity	1.12	0.93	1.35	ns
Hypothyroidism	1.68	0.99	2.84	0,06
CRF	0.72	0.46	1.13	ns
Angina or equivalent conditions	0.57	0.44	0.72	<0.001
Ischemia-inducing test (+)	0.86	0.74	1.01	0,06
Health insurance	0.89	0.77	1.02	ns

HT: Hypertension. DLP: dyslipidemia. DM: diabetes mellitus. S: smoking. CRF: Chronic renal failure. ns: Not significant.

The overall "normal" CA average in our group of patients (38.6%) agrees with data more recently reported in one registry from the United States and one from Canada (39.2% and 41.9%, respectively). (4, 5) We must emphasize that we excluded those patients who had no symptoms or noninvasive studies compatible with coronary ischemia. This subgroup (n = 1,006 patients) might include patients with no CA indication according to current guidelines. Furthermore, a particularly high proportion of normal CA can be seen in this type of patients, 61% in our case. (7)

The multivariate model showed that female gender was a strong predictor (OR: 4.2; 95% CI 3.62 - 4.95) of "normal" CA. This is consistent with a study conducted in 2011 by Schwalm et al., where the results of 24,637 patients submitted to CA evaluation for stable or unstable ischemic heart disease, showed that the rate of non-obstructive CAD was up to 43.5% in female versus 26.4% in male patients. (14) Considering

that in our study 57.7% of women showed this finding, perhaps a differential diagnostic algorithm for each sex should be established, to allow the physician to have a greater number of elements to indicate CA to a female patient. We believe that this could equate, at least, the efficacy observed with the use of CA in the male population.

In our study we observed that patients with “normal” CA are less likely to present traditional cardiac risk factors such as smoking, diabetes and hyperlipidemia. Extracardiac vascular disease and CRF were not independent predictors of “normal” CA. The data contrast with the results of similar and larger studies, which could be due to underreporting of these parameters in our study. (4, 5) We could also observe that the absence of symptoms interpreted by referral physicians as angina or equivalent conditions was important for predicting a “normal” CA (see Table 2). In 37.1% of patients with a positive ischemia-inducing test CA was “normal”, and this value rose to 43.5% when there were no associated symptoms. This seems to show the limitations of noninvasive tests when they are used as the sole method for identifying coronary patients. Diamond and Forrester proved in the 70s the strong relationship between symptoms and CAD (15). This highlights the importance of a thorough clinical history and the benefit that can be achieved by appropriate assessment of cardiac symptoms, even though there is evidence of the great variation in the ability of cardiologists to obtain an adequate characterization of ischemic chest pain. (16) CT angiography could occupy a place of special relevance both in women and in the subgroup of patients with an abnormal ischemia-inducing test as sole diagnostic element, since previous studies showed a better cost-benefit relation with the use of this method. (17)

Stratification of patients at risk of CAD aims to properly classify people who are more likely to benefit with a CA. (18, 19) Our study suggests that careful attention to the quality of cardiac symptoms and the absence of conventional cardiac risk factors may help identify those with higher probability of having a “normal” CA, especially in women. Strict compliance of current recommendations to indicate CA, associated with the use of conventional risk models, may help to stratify patients most likely to present with a “normal” CA.

A low number of patients with only moderate CA lesions (7.9%) were referred by interventional cardiologists. This group could benefit from a functional assessment by measuring fractional flow reserve in order to establish whether or not revascularization is necessary. (20, 21)

Evidence of hypothyroidism association with cardiovascular disease and atherosclerosis arises mainly from autopsy studies. Hypothyroid patients also present a higher proportion of cardiac events compared to euthyroid subjects. (22) Regarding subclinical hypothyroidism, numerous observational studies sug-

gest that this relationship also exists, although there is no controlled study demonstrating an association between mild hypothyroidism and cardiovascular disease. (23-33) This condition, which was not evaluated in more recent similar studies, showed a tendency to predict “normal” CA (OR: 1.68; 95% CI 0.99 to 2.84).

Due to the lack of similar studies in our country, these findings may be useful to clinicians interested in developing clinical strategies to reduce the frequency of normal CA.

In our study, absence of a positive ischemia-inducing test evidenced a not significant association with angiographically “normal” coronary arteries ($p = 0.06$). This could be due to the fact that ischemia-inducing tests (gamma camera, stress echo or graded exercise stress test) with different sensitivity and specificity for detecting significant CAD were included regardless of their different features.

Limitations

Our study has some limitations. Firstly, we have no information about the large population evaluated that did not receive CA indication, so a pattern of referral cannot be precisely established. Secondly, the interpretation of stress test results was determined based on the availability of studies performed at the time of CA. In no case data concerning the extent of ischemia or whether it was a high risk study was collected. Finally, both risk factors and history of previous diseases, whether cardiovascular or not, and the presence of symptoms were documented by the interventional cardiologist based on the report sent by the attending physician and the interview conducted prior to cardiac catheterization.

CONCLUSIONS

We observed that in a population referred for CA with stable CAD diagnosis, female gender, younger age and absence of symptoms were related to angiographically “normal” coronary arteries; whereas history of smoking, dyslipidemia and diabetes were inversely associated with this finding.

Although most patients with suspected chronic stable CAD had positive results in the ischemia-inducing test, no angiographic evidence of significant lesions was observed in a considerable number of them.

A better use of clinical stratification models could optimize CA performance to detect patients with significant CAD, limiting unnecessary studies.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms in the web / Supplementary Material).

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