Risk Factors and Extension of Ischemic Heart Disease Assessed by Non-Invasive Coronary Angiography

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SUMMARY

Background
Although several studies have well established the association between risk factors (RFs) and cardiovascular events, the relationship between the total extension of coronary atherosclerosis and RF has not been clearly determined yet.

Objective
The aim of this study was to assess the relationship between traditional coronary risk factors with the presence and extension of coronary atherosclerosis using high-resolution multislice computed tomography (MSCT).

Material and methods
We conducted a monocenter and observational study on consecutive patients in sinus rhythm who underwent multislice computed tomography coronary angiography. The population was prospectively categorized in three groups according to the number of RFs.

Results
One hundred and seventeen patients were included. Mean age was 58.5 ± 10.6 years, 81% were men and 19 suffered from diabetes.
A positive association was observed between the number of RFs and the prevalence of any lesion ($p = 0{,}001$), of significant lesions ($p < 0.001$), of multiple non significant lesions ($p< 0.001$) and of multiple significant lesions ($p < 0.001$). The number of lesions (1.9 ± 2.3 versus 4.3 ± 3.3 versus 6.6 ± 2.6, $p < 0{,}001$), and the calcium score [2.79 (0.0; 44.0) versus 64.0 (0.0; 273.2) versus 539.0 (74.0; 1,405.9), $p = 0.001$] were significantly greater in patients with multiple RFs.
Several RFS were individually associated with the presence of lesions. Age, diabetes, hypercholesterolemia, hypertension, a history of previous myocardial infarction and smoking habits were related to the presence of atherosclerosis, either by the evidence of a greater prevalence of lesions, of greater total number of lesions ad/or higher calcium scores.

Conclusions
This study found a significant relationship between the number of risk factors, as well as several risk factors per se, and the extension of coronary atherosclerosis assessed by multislice computed tomography coronary angiography

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Key words > Tomography, X-Ray Computed - Multislice - Atherosclerosis - Epidemiology

Abbreviations >

MSCT:	Multislice computed tomography	**BMI**	Body mass index
RF	Risk factor	**IVUS**	Intravascular ultrasound

BACKGROUND

From 1980 to 2000, age-adjusted cardiovascular mortality decreased from 543 to 267 per 100.000 inhabitants, and half of this reduction is related to a modification in risk factors (RFs). (1)

Several clinical and histopathology studies have demonstrated a clear association between traditional risk factors (RFs) and the presence, composition and extension of coronary and peripheral atherosclerosis. (1-5) This relationship has been explored in post mortem histopathology studies, while clinical studies

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have been performed with several invasive and non-invasive methods, such as quantitative coronary angiography, electron beam CT, carotid intima-media thickness and intracoronary ultrasound. The latter has recently become the gold standard for the assessment of the presence and extension of atherosclerotic coronary disease. (6-8) Nevertheless, although intracoronary ultrasound has been used to assess the anatomy of the entire coronary tree, this invasive procedure may fail to evaluate small vessels and distal beds. (6)

Multislice computed tomography (MSCT) coronary angiography has been recognized as an effective non-invasive tool for the diagnosis of obstructive atherosclerotic coronary disease. (9, 10) Recently, MSCT coronary angiography has proved its ability to describe the extension and distribution of non-obstructive lesions of the coronary tree. (11, 12)

The aim of this study was to assess the relationship between traditional coronary risk factors with the presence and extension of coronary atherosclerosis using high-resolution MSCT coronary angiography.

METHODS

Population

Patients eligible for this observational unicenter study were outpatients in sinus rhythm who were able to hold breath for 15 seconds or more, with no previous history of allergy to radiocontrast media, renal failure (serum creatinine > 1.4 mg/dl), coronary artery by-pass graft surgery or arrhythmias. Patients with a heart rate > 70 bpm received 50 mg of oral atenolol one hour before the scan or 1 mg every 5 minutes of intravenous propranolol until a heart rate < 65 bpm was achieved (maximum dose 5 mg). Nevertheless, patients with a high heart rate were not excluded.

Diabetes was defined by the presence of any of the following: fasting glycemia = 126 mg/dl, history of the risk factor reported in the medical record or if the patient was currently under treatment for diabetes. Hypercholesterolemia was defined as a total cholesterol = 200 mg/dl, history of the risk factor reported in the medical record or if the patient was currently under treatment for hypercholesterolemia. Hypertension was defined as systolic blood pressure or diastolic blood pressure = 140/90 mg/dl, history of the risk factor reported in the medical record or if the patient was currently under treatment for hypertension. Smoking was defined as the presence of current smoking habits or if the patient had quitted smoking during the previous month. Patients with a body mass index (BMI) = 30 (kg/m2) were considered obese. Age = 65 years was also considered a risk factor.

The study population was prospectively categorized according to the number of RFs (0-1 RFs, 2-3 RFs, y 4-7 RFs), and age = 65, diabetes, hypertension, hypercholesterolemia, smoking, obesity and previous infarction were considered risk factors.

The Committee on Ethics of the institution approved the protocol which fulfills the principles of the Declaration of Helsinki; all patients signed the informed consent form.

MSCT Image Acquisition

Image acquisition was performed with a 40- or 64-slice multidetector computed tomography scan in 80 and in 37 patients, respectively (*Brilliance 40* y *Brilliance 64*, Philips Medical Systems, Cleveland, Ohio). A preliminary scan was performed without contrast injection to determine the total calcium burden (calcium score) of the coronary tree. Then a bolus of 80-120 ml of iodinated contrast agent (Optiray®, Ioversol 350 mg/ml, Mallinckrodt, St Louis, USA) was injected into the antecubital vein at a flow rate adjusted by sex, age, body mass index and heart rate. The scan parameters were as follows: slice collimation 40 × 0,625 mm and 64 × 0,625 mm, tube rotation time 0.4 seconds, tube voltage 120 kV, tube current 600-1,500 mAs and pitch 0.2. All image data acquisition was synchronized with the ECG signal to achieve motion-free images. The bolus track technique was used to initiate the imaging sequence when the contrast enhancement reached the level of the coronary arteries. This technique consists in selecting an area of interest (descendant aorta) until the contrast enhancement reaches a predefined value, measured in Hounsfield units. The time from the start of the injection to the peak contrast enhancement determines the scan delay after the initiation of contrast material administration. In this way, The CT is automatically started when coronary arteries enhancement reaches the predefined threshold.

MSCT Analysis

Initially, images were reconstructed in late diastole (70% of the R-R interval) and image quality was assessed in each coronary segment. If needed, changing the reconstruction to 30%, 40%, 70% and 80% of the R-R interval yielded an excellent image quality. Coronary segments were assessed using 3-D reconstructions, curved multiplanar reconstructions and maximum intensity projections, according to the classification of the American Heart Association. (13) Two-dimensional multiplanar reconstruction curves were used to assess to extension of coronary plaques, as well as the severity and distribution of the lesions.

Two experimented observers (G. A. R. G. and M. A. R.) evaluated the presence or the absence of coronary lesions (at least one non-significant or significant obstruction), non-significant multiple lesions (= 2 vessels), significant lesions (stenosis = 50%) and significant multiple lesions in the entire coronary tree. Patent stents were considered non-significant lesions. Calcium scoring (Agaston score) was estimated in all patients on a dedicated workstation (Philips Extended Brilliance Workspace), except on those with stents. Ejection fraction was calculated in a biplanar fashion with a dedicated workstation (Philips Extended Brilliance Workspace).

Statistical analysis

Discrete variables are presented as figures and percentages. Continuous variables are expressed as mean or median ± standard deviation (percentiles 25 y 75). Comparisons were performed with Student's *t* test for independent samples, ANOVA or chi square test as indicated. Bonferroni test was used for post hoc comparisons. Correlations between continuous variables were assessed by Pearson coefficient of correlation. A p value < 0.05 was considered statistically significant. Statistical analysis was carried out with the statistical software package SPSS, version 13.0 (Chicago, Illinois, USA).

RESULTS

One hundred and twenty three consecutive patients were included. Subsequently, 6 patients were excluded: 5 with a poor image acquisition and 1 with

infiltration of the venous access. Therefore, the population studied comprised 117 patients. Table 1 shows the demographic characteristics. Mean age was 58.5 ± 10.6 years, 81% were men and 19% had diabetes.

Mean heart rate was 60.4 ± 6.4 bpm and scan mean duration was 11.8 ± 2.1 seconds.

A total of 1638 segments were assessed and 63 segments (3.8%) were not analyzed due to poor quality of images, moving artifacts or defective distal opacification.

Thirty patients (26%) had normal coronary arteries, 87 patients (74%) presented an abnormal scan (with at least one lesion), 48 patients (41%) had significant lesions, 69 patients (59%) showed multiple non-significant lesions and 25 (21%) presented significant multiple lesions.

The number of RFs was as follows: 0-1 FR: 42 patients, 2-3 RFs: 57 patients and 4-7 RFs: 18 patients. The presence of segments not analyzed was more frequent among patients with multiple RFs (0.36 ± 0.8 versus 0.53 ± 0.9 versus 1.00 ± 1.2; p = 0.055).

A positive association was observed between the number of RFs and the prevalence of any lesion (p = 0.001), of significant lesions (p < 0.001), of multiple non-significant lesions (p< 0.001) and of multiple significant lesions (p < 0.001) (Figure 1). The number of lesions (1.9 ± 2.3 versus 4.3 ± 3.3 versus 6.6 ± 2.6, p < 0,001), and the calcium score [2.79 (0.0; 44.0) versus 64.0 (0.0; 273.2) versus 539.0 (74.0; 1,405.9), p = 0.001] were significantly greater in patients with multiple RFs (Figure 2 A and B).

Table 1. Demographic characteristics (n = 117)

Age (SD)	58.5 ± 10.6
Men n (%)	95 (81.2)
Diabetes n (%)	22 (18.8)
Hipertension n (%)	51 (43.6)
Hypercolesterolemia n (%)	63 (53.8)
Current smoking n (%)	15 (12.8)
Previous semoking n (%)	22 (18.8)
Previous AMI n (%)	23 (20.5)
Previous PTCA n (%)	46 (39.3)
BMI±SD n (%)	27.8 ±4.2
***Scan* parameters**	
Hear rate (bpm)	60.4 ±6.4
Scan (seg)	11.8 ±2.1
Volume (ml)	112.7 ±14.2
Flow rate (ml/seg)	6.3 ±0.3
mA	979.1 ±64.5
Clinical presentation	
Asymptomatic* n (%)	53 (45.3)
Stable angina n (%)	36 (30.8)
Unstable angina n (%)	4 (3.4)
Non-conclusive functional test** n (%)	24 (20.5)

Discrete variables are presented as figures and percentages. Continuous variables are expressed as means ± standard deviation. PTCA: Percutaneous transluminal coronary angioplasty. * Patients studied for control of *stent* patency or for *screening* due to the presence of multiple risk factors. ** Discrepancy between the clinical presentation and the result of the functional test

Correlations

A significant and positive correlation between the number of RFs and the number of lesions was observed (r = 0.50, p < 0.001). In addition, there was also a significant correlation – though weak – between the number of RFs and the calcium score (r = 0.39, p = 0.002).

However, no correlations were found between the number of RFs and the ejection fraction (r = -0.02, p = 0.86).

Dichotomized Analysis According to Each Risk Factor

Elder patients had a greater prevalence of any lesion (Table 2), of a total number of lesions and higher calcium scores than younger patients (Table 3).

No significant differences were observed among both sexes.

Diabetic patients presented a greater prevalence of multiple non-significant lesions, of total number of lesions and higher calcium scores (Tables 2 and 3).

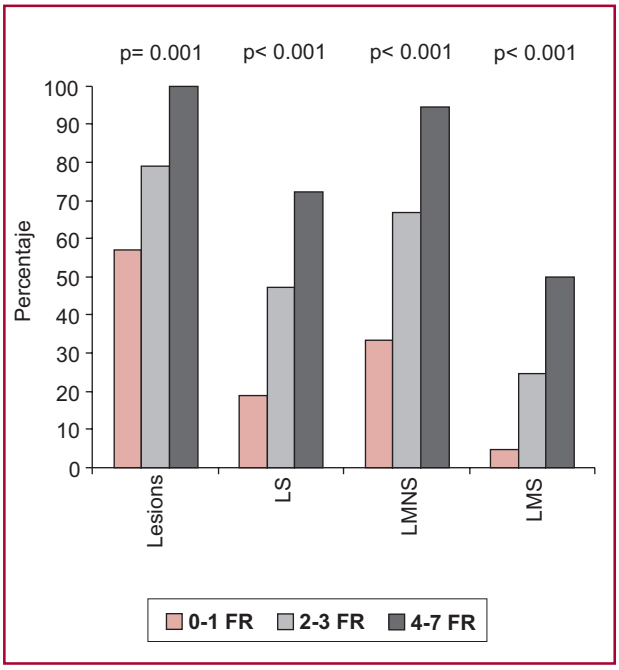

Fig. 1. Prevalence of patients with 0-1 risk factors, 2-3 risk factors and 4-7 risk factors with lesions in the coronary tree (p value calculated by chi square test). RF: Risk factor. SLs: Significant lesions. MNSLs: Multiple non-significant lesions. MSLs: Multiple significant lesions.

Hypertension was associated with a greater prevalence of any lesion and of multiple non-significant lesions, and hypertensive patients had a trend to present greater number of lesions and higher calcium scores (Tables 2 and 3).

Patients with dyslipemia had a greater number of lesions and higher calcium scores compared with patients without the RF (4.6 ± 3.4 versus 2.9 ± 3.0, p = 0.004 y 467.6 ± 908.0 versus 49.7 ± 103.1, p = 0.01, respectively)

Calcium scores were higher in obese patients than in non obese patients (635.2 ± 1,255.4 versus 146.8 ± 376.5, p = 0.02).

Patients with previous myocardium infarction presented a greater prevalence of any lesion, of significant lesions, of multiple non-significant lesions and of multiple significant lesions, as well as a greater total number of lesions (Tables 2 and 3).

Finally, smoking habit was associated with a greater total number of lesions (Table 3).

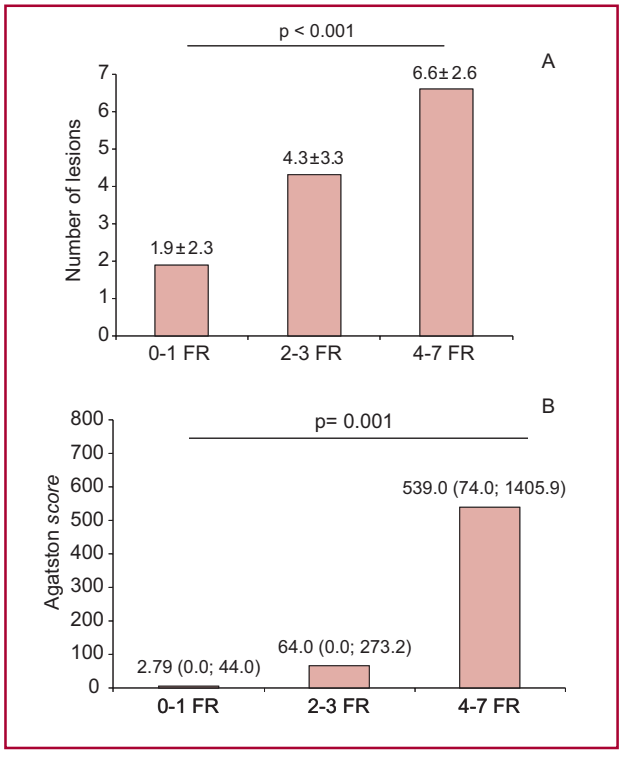

Fig. 2. Board A: Bar chart illustrating the relationship between the number of risk factors and the number of lesions. Board B: Bar chart illustrating the relationship between the number of risk factors and calcium score [expressed as median (interquartile range

DISCUSION

Several studies have recognized the presence of a clear association between coronary risk factors (RFs) and cardiovascular events; (14) however, the relationship between the extension of coronary atherosclerosis and the presence of RFs has not been categorically established.

Several clinical studies have been conducted to explore this association through diverse diagnostic methods, usually limited in their ability study the entire coronary tree. (2-5, 15)

It has been previously published that coronary angiography underestimates the extension and severity of coronary atherosclerosis (16, 17); however the usefulness of carotid intima-media thickness is limited, as the prevalence of RFs for atherosclerotic cardiovascular outcomes in the coronary arteries differs from other arterial territories. (18)

Electron beam CT scan was the first non-invasive procedure to estimate coronary calcium scoring for assessing the relationship between RFs and coronary atherosclerosis. (3)

Nevertheless, as coronary calcification is a late event during the atherogenic process this method does not represent the total atherosclerotic burden in the coronary arteries. (1)

Table 2. Percentage of lesions according to demographic characteristics

	Normal (%)	Lesions (%)	LSs (%)	MNS lesions (%)	MS lesions (%)
Age ≥ 65 años	6	94*	63*	88*	28
Men	23	77	43	61	23
Diabetes	14	86	55	77*	32
Hypertension	14	86*	43	73*	28
Hypercholesterolemia	21	79	52*	70*	32*
Obesity (BMI ≥ 30)	19	81	50	69	31
Current smoking	47	53	33	40	33
Previous smokin	9	91*	59	73	32
Previous AMI	0	100*	75*	88*	38*

P value calculated by chi-square test. SLs: Significant lesions. MNS: Multiple non-significant. MS: Multiple significant. BMI: Body mass index. * p < 0,05.

Tabla 3. Number of lesions, calcium score and ejection fraction categorized according to the presence or absence of risk factors

N° de lesiones (p/ANOVA)	Puntaje de calcio (p/ANOVA)	Fracción de eyección (p/ANOVA)	
Age ≥ 65 *versus* < 65	5.9 ± 3.0 / 3.0 ± 3.1 (< 0.01)	741.9 ± 1.324.8 / 160.4 ± 396.2 (0.01)	57.9 ± 10.8 / 58.2 ± 6.0 (0.87)
Male *versus* female	4.0 ± 3.3 / 3.1 ± 3.3 (0.26)	213.1 ± 435.8 / 597.6 ± 1.573.8 (0.51)	57.8 ± 7.9 / 59.5 ± 5.2 (0.40)
DM *versus* non DM	5.0 ± 3.1 / 3.5 ± 3.3 (0.05)	823.2 ± 1338.1 / 143.2 ± 357.7 (0.002)	59.3 ± 6.8 / 57.9 ± 7.7 (0.47)
HT *versus* non HT	4.4 ± 3.1 / 3.4 ± 3.4 (0.09)	451.1 ± 955.7 / 120.1 ± 301.8 (0.06)	58.9 ± 8.8 / 57.4 ± 6.0 (0.32)
DLP *versus* non DLP	4.6 ± 3.4 / 2.9 ± 3.0 (0.004)	467.6 ± 908.0 / 49.7 ± 103.1 (0.01)	58.6 ± 7.8 / 57.7 ± 7.2 (0.56)
BMI ≥ 30 *versus* BMI < 30	4.3 ± 3.2 / 3.5 ± 3.3 (0.31)	635.2 ± 1.255.4 / 146.8 ± 376.5 (0.02)	58.2 ± 8.2 / 58.2 ± 6.4 (0.99)
Current/previous/never SMK	2.7 ± 3.5 / 5.4 ± 3.8 / 3.6 ± 3.0 (0.03)	87.2 ± 181.3 / 183.1 ± 234.4 / 323.1 ± 806.3 (0.56)	58.0 ± 10.2/ 59.1 ± 4.1 / 57.9 ± 7.7 (0.82)
Previous *versus* non-previous AMI	6.3 ± 2.6 / 3.2 ± 3.2 (< 0.01)	611.1 ± 726.5 / 238.3 ± 676.2 (0.29)	52.9 ± 9.4 / 59.5 ± 6.3 (< 0.001)

DM: Diabetes mellitus. HT: Hypertension DLP: Dyslipidemia. BMI: Body mass index. SMK: Smoker. AMI: Acute myocardial infarction. Continuous variables are presented as means ± standard deviation.

Intravascular ultrasound (IVUS) is an invasive diagnostic tool useful for the assessment of the presence of coronary atherosclerosis and its extension, which has been recently incorporated to this study field and has identified several RFs as independent predictors of the coronary atherosclerotic burden. (4)

Nevertheless, as IVUS explores only a part of the coronary tree, it does not always reflect the total atherosclerotic burden in the coronary arteries. (6)

As far as we know, our study is the first in reporting the relationship between traditional coronary risk factors and the extension of coronary atherosclerosis by non invasive coronary angiography with multislice computed tomography.

This method screened almost the entire coronary tree (only 3% of the segments were excluded), resulting in a more precise assessment of this association.

In this way, we found a significant relationship between the number of RFs and the presence and extension of coronary atherosclerosis, and this relationship is also present when several RFs are individually analyzed.

The prevalence of atherosclerotic lesions was highly related with the number of RFs. Similarly, the total number of lesions and the extension of coronary calcifications were significantly greater in patients with multiple RFs.

Several RFs were associated per se with the presence of lesions. Age, diabetes, hypercholesterolemia, hypertension, a history of previous myocardial infarction and smoking habits were related to the presence of atherosclerosis, either by the evidence of a greater prevalence of lesions, a greater total number of lesions ad/or higher calcium scores.

An international registry has recently reported the prevalence of different RFs in patients with ischemic heart disease: 38% had diabetes, 80% hypertension, 77% dyslipemia, 45% obesity and 13% were smokers. (19)

In light of the recent evidence regarding the prognostic value of non-invasive coronary angiography with multislice computed tomography for prediction of all-cause mortality (20), our findings should contribute to maximize preventive measures to reduce the prevalence of risk factors and, consequently, the atherosclerotic coronary burden.

Limitations

A selection bias may not be ruled out due to the small number of the sample. Serum determinations of cholesterol, C reactive protein, homocysteine or lipoprotein (a) have not been performed. Finally, the severity of the lesions has not been compared to conventional coronary angiography, considered the gold standard; therefore the results based on analysis that have used this secondary outcome should be considered exploratory.

CONCLUSIONS

This study found a significant relationship between the number of risk factors, as well as several risk factors per se, and the extension of coronary atherosclerosis assessed by coronary angiography with multislice computed tomography.

RESUMEN

Antecedentes

A pesar de que numerosos estudios han establecido una clara asociación entre los factores de riesgo (FR) y los eventos cardiovasculares, la relación entre la extensión total de la aterosclerosis coronaria y los FR no se ha establecido categóricamente.

Objetivo

Explorar la relación entre factores de riesgo coronario tradicionales y la presencia y extensión de aterosclerosis coronaria mediante angiografía coronaria por tomografía computarizada multicorte (ACTCM) de alta resolución.

Material y métodos

En este estudio monocéntrico observacional, pacientes consecutivos en ritmo sinusal se estudiaron mediante angiografía coronaria por tomografía computarizada

multicorte. La población se categorizó prospectivamente en tres grupos de acuerdo con el número de FR.

Resultados

Se incluyeron en el estudio 117 pacientes. La edad media fue de 58,5 ± 10,6 años, el 81% eran hombres y el 19% eran diabéticos.

Se observó una correlación significativa entre la prevalencia de cualquier lesión (p = 0,001), de lesiones significativas (p < 0,001), de múltiples lesiones no significativas (p < 0,001) y de múltiples lesiones significativas (p < 0,001) y el número de FR. En paralelo, tanto el número de lesiones (1,9 ± 2,3 *versus* 4,3 ± 3,3 *versus* 6,6 ± 2,6, p < 0,001) como el puntaje de calcio [2,79 (0,0; 44,0) *versus* 64,0 (0,0; 273,2) *versus* 539,0 (74,0; 1.405,9), p = 0,001] fueron significativamente mayores en pacientes con múltiples FR.

Individualmente, numerosos FR se asociaron con la presencia de lesiones. La edad, la diabetes, la hipercolesterolemia, la hipertensión, el antecedente de IAM y el tabaquismo se encontraron relacionados con la presencia de aterosclerosis, ya sea por evidenciar mayor prevalencia de lesiones, mayor número total de lesiones y/o mayor puntaje de calcio.

Conclusiones

En el presente estudio se encontró una relación significativa entre el número de factores de riesgo, así como de numerosos FR *per se*, y la extensión de la aterosclerosis coronaria evaluada mediante angiografía coronaria por tomografía computarizada multicorte.

Palabras clave > Tomografía computarizada por rayos X - Multicorte - Aterosclerosis - Epidemiología

Competing interests

None declared.

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