

Clinical and angiographic assessment of coronary bare-metal stent restenosis

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PTCA: Percutaneous transluminal coronary angioplasty

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ABSTRACT

Introduction: Ischemic heart disease is the leading cause of death in Cuba. Coronary angioplasty with stenting is an excellent treatment option, but restenosis overshadows its prognosis and is more common with the use of bare metal stents.

Objective: To characterize restenosis after coronary bare-metal stent from the clinical and angiographic points of view.

Method: A descriptive cross-sectional study was conducted in 59 patients with a diagnosis of restenosis after coronary bare-metal stent confirmed by angiography in the Interventional Cardiology Unit of Cardiocentro Ernesto Che Guevara of Villa Clara, Cuba, from February 2010 to April 2012. The variables analyzed were age, sex, coronary risk factors, previous history of angina or heart attack, vessel involved, type of restenosis and treated lesion, vessel diameter and lesion length.

Results: Predominance of male patients (76.27 %), aged 60-69 years (40.66 %). The most common risk factors were hypertension (76.27 %), smoking (37.28 %) and type II diabetes mellitus (33.89 %). The most affected vessel was the left anterior descending (28.81 %), arterial diameters were predominantly ≤ 2.5 mm (54.2%) and lesion length > 20 mm (65, 97). Type B injuries (52.5) and focal restenosis (57.62 %) were more frequent.

Conclusions: Patients with restenosis were predominantly male, between 60-69 years old, with a history of hypertension, smoking and diabetes mellitus type II. Left anterior descending disease, diameter ≤ 2.5 mm, lesion length > 20 mm, type B coronary lesion and focal restenosis were more frequent.

Key words: Coronary artery disease, Angioplasty, Bare metal stent, Restenosis, Risk factors

Valoración clínica y angiográfica de la reestenosis del stent coronario convencional

RESUMEN

Introducción: La cardiopatía isquémica es la principal causa de muerte en Cuba. La angioplastia coronaria con *stent* es una excelente opción terapéutica, pero la reestenosis ensombrece su pronóstico y es mucho más frecuente con el uso de *stents* convencionales.

Objetivo: Caracterizar clínica y angiográficamente la reestenosis del *stent* coronario convencional.

Método: Se realizó un estudio descriptivo y transversal en los 59 pacientes con diagnóstico de reestenosis del *stent* coronario convencional confirmado por angiografía en la Unidad de Cardiología Intervencionista del Cardiocentro “Ernesto Che Guevara” de Villa Clara, Cuba, durante el período febrero 2010 – abril 2012. Las variables analizadas fueron edad, sexo, factores de riesgo coronario, historia previa de angina o infarto, vaso afectado, tipo de reestenosis y de lesión tratada, diámetro del vaso y longitud de la lesión.

Resultados: Predominaron los pacientes del sexo masculino (76,3 %), con edades comprendidas entre 60-69 años (40,7 %). Los factores de riesgo más frecuentes fueron la hipertensión arterial (76,3 %), el hábito de fumar (37,3 %) y la diabetes mellitus tipo II (33,9 %). El vaso más afectado fue la descendente anterior (59,3 %), los diámetros arteriales eran predominantemente $\leq 2,5$ mm (54,2 %) y la longitud de las lesiones > 20 mm (66,1 %). Las lesiones tipo B (52,5 %) y la reestenosis focal (57,6 %) fueron más frecuentes.

Conclusiones: Los pacientes con reestenosis eran predominantemente hombres, entre 60-69 años de edad, con antecedentes de hipertensión arterial, tabaquismo y diabetes mellitus tipo II. La enfermedad de la descendente anterior, el diámetro del vaso $\leq 2,5$ mm, la longitud de las lesiones > 20 mm, la lesión coronaria tipo B y la reestenosis focal fueron más frecuentes.

Palabras clave: Cardiopatía isquémica, Angioplastia coronaria, *Stent* convencional, Reestenosis, Factores de riesgo

INTRODUCTION

Ischemic heart disease is a major cause of morbidity and mortality worldwide. In Cuba it represents about 75 % of cardiovascular disease and about 25 % of overall mortality¹. Its main cause is coronary atherosclerosis, which is a multifactorial disease and appears by the association of multiple coronary risk factors (CRF) producing vascular endothelium disorders, which leads to the accumulation of lipids, macrophages, platelets and T lymphocytes in the subintimal space and stimulate the migration and proliferation of smooth muscle cells, with extracellular matrix formation originating atheroma²⁻⁴.

These plaques, which may have different dimensions, present concomitant degrees (total or partial) of arterial obstruction, may be vulnerable or not, and lead to the corresponding stages of the disease clinical expression^{4,5}.

Percutaneous transluminal coronary angioplasty (PTCA) is an excellent treatment option for patients with chronic stable angina or any type of acute coronary syndrome. This therapeutic modality, with stent implantation has reduced mortality from acute myocardial infarction (AMI) and maintained patency of the affected vessel, ensuring the mechanical support that prevents elastic recoil of the wall of the artery treated with the consequent reduction of recurrent ischemia

and cardiac arrhythmias, all with a short hospital stay^{6,7}.

Since stents were first used in Palmaz Schatz, in the late '80s and to the present, the changes in their structures have been impressive, as an evidence of the evolution of new and more sophisticated geometric shapes, with less material in its metal structure that will not weaken its radial strength but also maintain and even increase its flexibility, all of which gives stents ever better features to favor its implantation in increasingly tortuous and distal arteries⁶⁻⁹.

Simultaneous to this development, drug-eluting stents have emerged and developed, which have a polymer on its metal frame, wherein an antiproliferative substance (sirolimus or paclitaxel and its analogs) is placed that significantly reduces the risk of restenosis. But its high cost prevents widespread use in developing countries such as Cuba, where only a few series of patients with this type of device have been reported, and where the use of bare-metal stents predominates⁹.

Restenosis usually occurs in the first 6 months after PTCA has been performed and its frequency has ranged from 30-45 % in the beginning, to 15-20 % in the current era⁹⁻¹¹.

The coronary stent implantation has helped improve the restenosis rate by controlling two of the components of the vascular response: early elastic recoil and late vascular constriction. However, intimal proliferation seems to be exacerbated after stent implantation. The most frequently associated predictive factors are diabetes mellitus, increased length of the lesion treated, history of prior revascularization (either percutaneous or surgical), a smaller reference diameter of vessel, location in the left anterior descending artery and a smaller lumen diameter after the procedure^{12,13}.

The objective of this research was to characterize coronary bare metal stent restenosis compared to clinical and angiographic variables.

METHOD

A descriptive cross-sectional study was performed in 59 patients with a diagnosis of restenosis of coronary stents in the Interventional Cardiology and Catheterization Unit of Cardiocentro Ernesto Che Guevara,

in Santa Clara, Villa Clara, Cuba, from February 2010 to April 2012.

Inclusion criteria

All patients with coronary artery disease undergoing PTCA in the period mentioned, who presented coronary stent restenosis were included.

Technique description

Conventional coronary angiography via femoral was performed to the 59 patients who had showed myocardial ischemia in any of the usual tests for this purpose. PTCA was performed there and then. The stenting procedure was guided by the visual analysis of angiograms. Once PTCA was initiated an unfractionated sodium heparin bolus was administered at 100 IU/kg. PTCA catheter was passed with the stent until it was placed in the injury site; its full expansion was achieved by inflating the balloon to pressures equal or greater than 14 atmospheres, depending on vessel diameter and hardness of the lesion.

Information collection

The primary data was collected through a questionnaire prepared for this purpose, through the interview, medical history of patients and the reports of the Interventional Cardiology Unit. The variables were: age (in years), sex (male or female), CRF (hypertension, diabetes mellitus, dyslipidemia, smoking, obesity)^{2,4,14,15}, previous history of angina or AMI, affected vessel (left anterior descending, circumflex, right coronary artery), type of restenosis (focal or diffuse)^{12,16,17}, vessel diameter and lesion length (in millimeters), and type of lesion (A, B, C)¹⁷.

Statistical analysis

The collected data were entered and processed using the SPSS statistical software, version 15.0. Absolute frequencies (number of cases) and relative (percentage) were determined.

For the analysis and interpretation of results, statistical techniques according to a descriptive study design were used, which included the test of homogeneity of independent groups and goodness of fit test for the comparison of percentages based on the Chi-squared distribution.

As a result of these statistical hypothesis tests, the value of the corresponding statistic for its p significance (value) was presented. According to the p value, the difference or association was classified as significant ($p < 0.05$) and not significant ($p \geq 0.05$).

Bioethical considerations

Although no personal information from patients or relatives was required, the research complied with the 5 ethical principles and confidentiality of data was guaranteed. This study was approved by the Research Ethics Committee of the Cardiocentro Ernesto Che Guevara.

RESULTS

The distribution of patients by sex and age groups (Table 1) shows that there is a male predominance with a total of 45 patients (76.3%) and the most affected age group was between 60-69 years (40.7%). Only 14 women (23.7 %) had restenosis, without clear

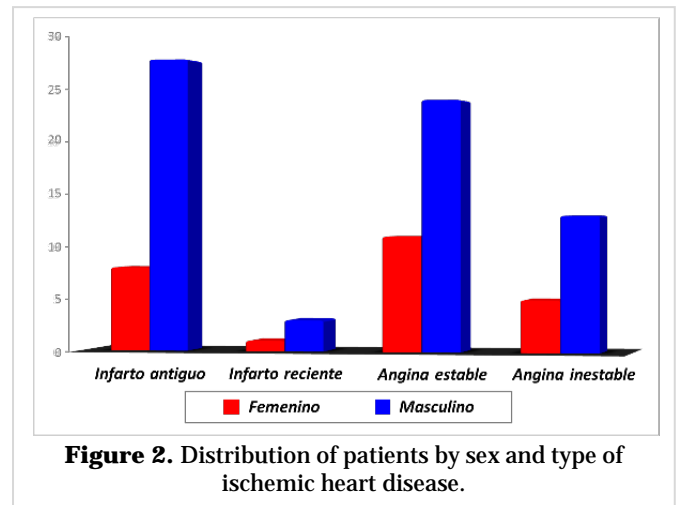
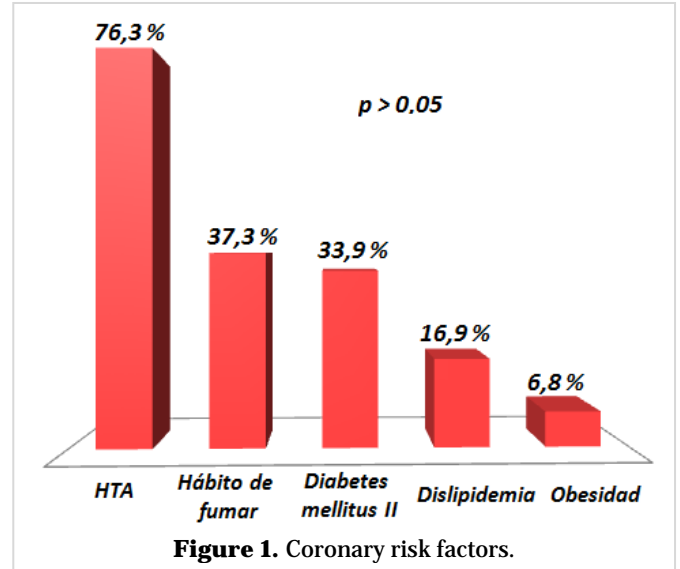


Table 1. Distribution of patients by sex and age groups.

Age groups (years)	Sex				Total	
	Female		Male		Nº	%
	Nº	%	Nº	%		
< 40	1	1,7	1	1,7	2	3,4
40 - 49	2	3,4	7	11,9	9	15,2
50 - 59	4	6,8	12	20,3	16	27,1
60 - 69	4	6,8	20	33,9	24	40,7
≥ 70	3	5,1	5	8,5	8	13,6
Total	14	23,7	45	76,3	59	100

$\chi^2=2.29$; $p=0.683$

Source: Interventional Cardiology and Catheterization Unit Database. Cardiocentro Ernesto Che Guevara. Villa Clara, Cuba.

predominance among age groups. Although there were three times more men than women, there were no significant differences in general ($p=0.683$).

The most frequent coronary risk factor was high blood pressure (Figure 1), present in 45 of patients studied (76.3%), followed by smoking (37.3%), diabetes mellitus (33.9%), dyslipidemia (16.9%) and obesity in a lower percentage (6.8%). There were no significant differences in distribution by sex.

The distribution of patients according to sex and type of ischemic heart disease (Figure 2) shows that old infarction (28 males and 8 females) and stable angina (24 men

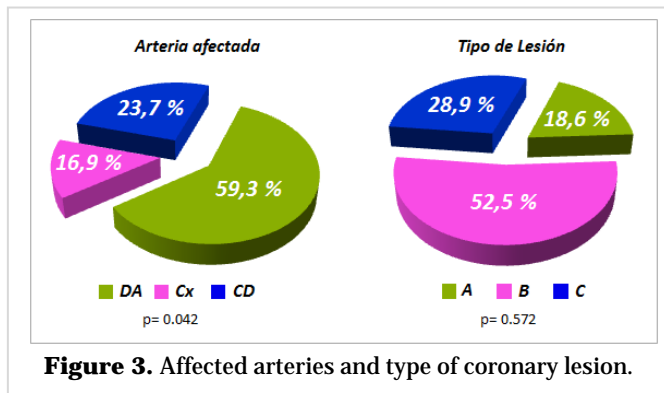


Figure 3. Affected arteries and type of coronary lesion.

and 11 women) predominated. A minority of cases had suffered a recent infarction. Male predominance in all types of ischemic heart disease studied is clearly evident.

Figure 3 shows that the left anterior descending artery (59.3%), followed by the right coronary (23.7%) and the circumflex (16.9%), were the most affected arteries by restenosis with significant differences ($p = 0.042$). And the types of lesion treated on restenosis occurred were, B (52.5%), C (28.9%) and A (18.6%) in

order of frequency.

Other data show that the most affected segments were the middle of the anterior descending artery (28.8%), followed by the proximal of right coronary artery (14.6%), and distal of circumflex artery (11.3%).

Vessel diameter ≤ 2.5 mm and lesion length of > 20 mm (42.4%) predominated, followed by diameter of 2.6 - 3,0 mm and > 20 mm of lesion length (18.6%), where significant differences $p = 0.028$ (**Table 2**) were found. Note that there were no patients with small lesions and good vessel caliber.

When age groups and type of restenosis were compared (**Table 3**) no significant differences were found ($p = 0.937$). There was a predominance of focal restenosis with a total of 34 patients (57.6%), and the age group 60-69 years was more frequently affected (40.6%), followed by those aged 50-59 (27.1%).

The association between restenosis and CRF (**Table 4**) showed no significant differences either ($p = 0.561$). The percentages were similar in the assessed CRF except in patients with dyslipidemia, where focal restenosis predominated (8 of 10 patients), representing 13.6% of all patients and 80% of those with this lipid disorder.

Of the 59 patients with restenosis, the new percutaneous revascularization could only be performed in 28 patients, 17 stent PTCA (stent-intrastent) and 11 balloon PTCA. Of the remaining 31, 28 were referred to surgery and 3 remained with medical therapy, due to the comorbidities and high preoperative risk, pending the implantation of a drug-eluting stent.

Table 2. Distribution of patients, according to vessel diameter and lesion length.

Vessel diameter (mm)	Lesion length (mm)						Total	
	< 10		10 - 20		> 20			
	Nº	%	Nº	%	Nº	%	Nº	%
$\leq 2,5$	0	0	7	11,9	25	42,4	32	54,2
2,6 - 3,0	0	0	9	15,2	11	18,6	20	33,9
$> 3,0$	0	0	4	6,8	3	5,1	7	11,9
Total	0	0	20	33,9	39	66,1	59	100

$\chi^2=2.852$; $p=0.028$

Table 3. Distribution of patients by age and type of restenosis.

Age groups (years)	Restenosis		Total	
	Focal	Diffuse	Nº	%
< 40	1	1	2	3.4
40 - 49	6	3	9	15.2
50 - 59	8	8	16	27.1
60 - 69	14	10	24	40.7
≥ 70	5	3	8	13.6
Total	34 (57,6 %)	25 (42,4 %)	59	100

$\chi^2=0.813$; $p=0.937$

DISCUSSION

The predominance of males can be attributed to the small sample size, because although ischemic heart disease predominates in men at younger ages, this difference is equated as age advances, after a woman loses estrogen protection. Regarding the predominating age group, our results are consistent with the literature¹⁸⁻²⁰, as this disease is more common in patients older than 60 years. In fact,

Table 4. Distribution of patients according to risk factors and restenosis rate (n=59).

Risk Factors	Restenosis				Total	
	Focal		Diffuse		Nº	%
	Nº	%	Nº	%		
Hypertension	23	38,9	22	37,3	45	76,3
Type II diabetes mellitus	12	20,3	8	13,6	20	33,9
Smoking	12	20,3	10	16,9	22	37,3
Dyslipidemia	8	13,6	2	3,4	10	16,9
Obesity	2	3,4	2	3,4	4	6,8

$\chi^2=2.98$; $p=0.561$

most of the new cases are seen in patients over 65 years, especially in females^{20,21}.

Ischemic heart disease in women has a similar incidence as in men, but with 6-10 years of delay, so that from 70-75 years it is essentially the same. This fact, known since the '50s of last century, has caused to consider the hypothesis of a protective effect of estrogen^{22,23}.

In a study performed in Hermanos Amejeiras Hospital, in Havana, Cuba, that aimed to characterize the behavior of the different variables of clinical restenosis, male gender and the age group of 50-59 years were found to be the most affected¹⁷. Previous studies have indicated that male gender is an independent factor of poor prognosis²⁴.

Hypertension is an important CRF and could be a contributing factor in stent restenosis, which is the Achilles heel of interventional cardiology⁹. In this research, a high prevalence of hypertension was observed, which is in line with the epidemiological profile of the current Cuban population and the frequent association of this disease with the coronary atherosclerosis^{9,17}.

Diabetes mellitus has been the most described clinical predictive factor because of a greater hyperplastic response of the vascular wall²⁵⁻²⁷, but this does not correspond with our results, which is also due to the small sample size and to the fact that many diabetic patients are referred to surgery. Many of the mechanisms described, favoring both restenosis and progression of coronary artery disease in diabetics, dependent on hyperglycemia and on the coexistence of other risk factors^{27,28}. However, in the study by Jiménez-Quevedo *et al.*²⁹, diabetes was not significantly associated with restenosis. Other studies indicate

that restenosis is common in insulin-dependent diabetics, for, in general, these patients have diffuse and small vessel disease²⁹⁻³⁰.

López y Cortés-Bergoderi³¹ did not find that dyslipidemia and obesity constitute significant clinical variables of restenosis. However, another study of clinical predictors³² found that of all patients with restenosis, 21.6% were diabetic, 59.2% hypertensive, 25.5% dyslipidemic, and

37.5% active smokers.

Although obesity is an independent risk factor for cardiovascular disease, no relation with restenosis³¹, has been found which coincides with our results.

The findings of this study on the prevalence of CRF are consistent with other national and international research^{9,24,30,33-36}. Hypertension is a global health problem; in Cuba its prevalence in patients who had undergone coronary angiography is high⁹. According to Byrne *et al.*³⁷, cardiac events following a successful coronary angioplasty were more frequent in hypertensive patients, and according to Alonso Martín *et al.*³⁸, hypertension and diabetes type II often coexist, with a prevalence of hypertension in diabetics approximately twice that in non-diabetics. Both CRF stimulate endothelial dysfunction (fundamental process that relates them to restenosis)^{9,39,40}. Type II diabetics may have a chance of 50% or more of angiographic restenosis, so it has been established that this disease is an independent and major risk factor for the development of this complication^{41,42}.

Most cases of Silber *et al.*⁴³ were referred for unstable angina and many of them had an association of three or more CRF. Ximenes Meireles *et al.*⁴⁴ observed that a history of AMI was present in 18.4% of patients, stable angina in 43.3% and 68.1% were male. And in a Cuban study, with the purpose of monitoring patients with Firebirg³⁰ stent, there was a male predominance and history of AMI in the 52 patients included.

In the studies of López Pérez *et al.*³⁰ and Byrne *et al.*³⁷, complex lesions predominated (B and C), which coincides with our results. The incidence of restenosis is closely related to PTCA and type of coronary lesion treated, the criteria in the guidelines of the American

College of Cardiology and the American Heart Association indicate moderate success (60-85%) in type B lesions and low (<60%) on the C⁴⁵⁻⁴⁷ type, although it must be acknowledged that most chronic total occlusions as well as long, angled and heavily calcified lesions are currently successfully treated, as technological advances and the emergence of new intravascular devices have facilitated our work.

Valencia *et al.*⁴⁸ studied patients with stenosis of the left anterior descending artery treated with stents and repeat revascularization rate was low, however, the propensity of this artery to restenosis is known, so the involvement of its proximal segment represents a special subset of patients. *In vivo* studies with intravascular ultrasound have shown a predominantly eccentric involvement of this type of injury^{43,48}. In our study the most treated ones were those of the middle segment with length > 20 mm. It is evident that the absence of patients with lesions smaller than 10 mm in our series is because, no matter the caliber of the vessel, these very short lesions are unlikely to restenosis.

Other anatomical factors have been associated with an increased risk of this complication. Various studies have identified a relationship between total occlusion and severe stenosis prior to angioplasty with the development of restenosis after the procedure. It has also been associated with long, eccentric, of proximal location, calcified, ostial and bifurcated lesions^{43,49}.

González *et al.*¹⁷ describe lesions of predominantly ostial location and in the anterior descending artery. When Astin and Jones⁵⁰ studied the evolution of these lesions they showed that stent expansion was lower in the branch, with greater neointimal hyperplasia in the ostium than in its distal segment or in the main vessel. They also stated that a minimal luminal area of less than 4.8 mm² in the ostium of the branch after PTCA, with subsequent neointimal growth, makes this the most frequent site of restenosis.

A significant association was found when vessel diameter and lesion length were related, which is consistent with various research^{18,41,51-55}, as it is acknowledged that these situations are predictors of restenosis. The smaller vessel size and the greater lesion length are independent risk factors of restenosis^{53,54}. This ratio decreases but does not disappear with the use of active drug-eluting stents^{10,11,56-59}.

According to Serruys *et al.*⁶⁰, 10-30% of diffuse le-

sions, greater than 20 mm need a new intervention during monitoring and Planas-del Viejo *et al.*⁵⁸ reported that over 30% of lesions commonly treated by PTCA correspond to small vessel disease.

With the current experience it has become clear that vessel diameter and lesion length are powerful predictors of restenosis^{23,44,61}.

Relationship with age has not been established. In our study no association was found either, however, depending on the type of injury and patient comorbidities different types of restenosis will be presented, although according to Byrne *et al.*³⁷ and Ximenes Meireles *et al.*⁴⁴ the focal pattern is predominant.

The fact that in this study only 29 patients underwent the new percutaneous revascularization is due to the limited availability of drug-eluting stents (bare-metal stent restenosis should not be treated with another of the same characteristics), and favorable results of coronary surgery at the hospital where the study was conducted.

Multiple factors have been associated with the incidence of restenosis, among them are clinical factors (diabetes mellitus, unstable angina, previous restenosis), angiographic (proximal left anterior descending artery, small vessel diameter, total occlusion, ostial disease, bifurcations, long lesion and saphenous vein graft) procedure-related (significant residual stenosis, smaller minimum luminal diameter, smaller acute postprocedural gain and prior restenotic behavior) and genetic factors^{47,49,59,62-68}.

New antiproliferative drugs are being investigated in order to reduce restenosis, stents with selective eluting systems and the ability to deliver different drugs, and biodegradable stents. Undoubtedly, the future development of these devices is wide and will surely benefit patients.

CONCLUSIONS

Patients with restenosis were predominantly male, between 60-69 years old, with a history of hypertension, smoking and diabetes mellitus type II. Left anterior descending disease, vessel diameter ≤ 2.5 mm, lesion length > 20 mm, type B coronary lesion and focal restenosis were more frequent.

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