Analysis of Differences in Flow-Mediated Dilation in Relation to the Treatment of Coronary Patients

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Introduction. Flow-mediated dilation (FMD) is thought to be related to the development of coronary disease. We were interested in knowing the degree of FMD in a large sample of coronary patients in relation to the therapy they were given in clinical practice.

Patients and method. We studied 1,081 coronary patients (age 68 ± 12 years, 73% male) in which FMD was evaluated in the brachial artery. The patients were classified into 5 treatment groups (416 who receive 2 or more treatments were excluded): group A: 81 controls treated with aspirin, group B: 198 treated with ACE inhibitors, group C: 106 with calcium antagonists, group D: 145 with β-blockers, and group E: 135 with lipid lowering medication (93% statins).

Results. ANOVA was used to analyze the differences between groups. With regard to the number of risk factors present in each group, the patients treated with ACE inhibitors (2.44 ± 0.79 vs 2.14 ± 0.89; $p < 0.05$) and statins (3.45 ± 0.70 vs 2.14 ± 0.89; $p < 0.05$) had more risk factors than GrA and higher levels of LDL-cholesterol (ACE inhibitors 145.0 ± 33.5 vs 128.5 ± 32.2 and statins 157.8 ± 45.3 vs 128.5 ± 32.2; $p < 0.05$). GrB had a higher glycemia than controls (123.4 ± 32.2 vs 114.7 ± 33.7; $p < 0.05$). The control group was younger than the therapeutic groups ($p < 0.05$). Compared with the control group, FMD was significantly higher only in the group treated with ACE inhibitors (3.42 ± 6.01 vs 0.82 ± 6.04; $p < 0.05$). Multivariate logistical regression showed that treatment with ACE inhibitors and statins ($p < 0.05$) were independent predictors of FMD > 4%.

Conclusion. Treatment with ACE inhibitors or statins was predictive of the normalization of FMD in coronary patients in clinical practice.

Key words: *Endothelium. Risk factors. Prevention. Drugs.*

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Análisis de las diferencias encontradas en la dilatación mediada por flujo según la terapia seguida en pacientes con enfermedad coronaria

Introducción. La dilatación mediada por flujo (DMF) ha sido propuesta como un marcador de enfermedad coronaria. Nuestro objetivo ha sido conocer el grado de DMF en una muestra amplia de enfermos coronarios según la terapia seguida en la práctica clínica.

Pacientes y método. Estudiamos a 1.081 pacientes coronarios (edad 68 ± 12; 73% varones) en los que se evaluó la DMF braquial. Según el tratamiento, los pacientes fueron clasificados en 5 grupos (fueron excluidos 416 pacientes con ≥ 2 terapias): grupo A, 81 controles tratados con aspirina; grupo B, 198 con IECA; grupo C, 106 con antagonistas del calcio; grupo D, 145 con bloqueadores beta, y grupo E, 135 tratados con fármacos hipolipemiantes (93% estatinas).

Resultados. Mediante ANOVA se analizaron las diferencias entre grupos. Respecto al número de factores de riesgo, los pacientes en tratamiento con IECA (2,44 ± 0,79 frente a 2,14 ± 0,89; $p < 0,05$) y estatinas (3,45 ± 0,70 frente a 2,14 ± 0,89; $p < 0,05$) presentaron un mayor número de factores de riesgo que el grupo A y valores más elevados de cLDL (IECA 145,0 ± 33,5 frente a 128,5 ± 32,2 y estatinas 157,8 ± 45,3 frente a 128,5 ± 32,2; $p < 0,05$). Además, el grupo B presentó valores superiores de glucemia que el grupo control (123,4 ± 32,2 frente a 114,7 ± 33,7; $p < 0,05$). La edad fue inferior en el grupo control que en el resto de grupos terapéuticos ($p < 0,05$). La DMF fue superior respecto el grupo control sólo en el grupo de tratamiento con IECA (3,42 ± 6,01 frente a 0,82 ± 6,04; $p < 0,05$). Mediante regresión logística multivariante se encontró que el tratamiento tanto con IECA como con estatinas ($p < 0,05$) es un predictor independiente de una DMF > 4%.

Conclusión. El tratamiento con IECA o estatinas es predictor de una mejor dilatación mediada por flujo en pacientes coronarios en la práctica clínica.

Palabras clave: *Endotelio. Factores de riesgo. Prevención. Fármacos.*

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ABBREVIATIONS

CAD: coronary artery disease.
FMD: flow-mediated dilation.
NMD: nitroglycerin-mediated dilation.
ACEI: angiotensin-converting enzyme inhibitors.

INTRODUCTION

Ever since the role of the endothelium as an essential organ in the control of vascular hemostasis and tone was confirmed,[1-3] various tests have corroborated its central role in the development of the atherosclerotic process.[4,5] We know that patients with coronary artery disease (CAD) present less favorable indicators of endothelial function and the role of each risk factor as a determinant of endothelial dysfunction.[6-10] Endothelial dysfunction has been associated with cellular adhesion and infiltration phenomena and oxidized low density lipoprotein (LDL) particles, factors that are involved in the process of development of CAD,[11] in addition to its destabilization.[12] The endothelium has functions in the control of coagulation and platelet aggregation, whose activation is related to the appearance of coronary complications.[13] Patients with acute coronary events present more advanced endothelial dysfunction than stable coronary patients.[14] This would explain why in two recent follow-up studies endothelial dysfunction was associated with a greater risk of coronary complications.[15,16]

Preventive measures center on the control of risk factors, as suggested by the Framingham Heart Study.[17] Secondary prevention intervention trials, principally with statins and, to a lesser extent, with angiotensin-converting enzyme inhibitors (ACEI) and calcium antagonists, have demonstrated an improved prognosis.[18-20] Some of these therapies can improve the grade of endothelial function.[21,22] Flow-mediated dilation (FMD) is a non-invasive, convenient, and economical method[23] that can bring us closer to understanding the state of peripheral endothelial function. In addition, FMD correlates with coronary endothelial function.[24] Our intention is to know the grade of FMD that coronary patients present in clinical practice according to the pharmacological therapy followed.

PATIENTS AND METHOD

Patients

Between January 1997 and March 2001, we studied 1081 patients, age 68±12 years, 73% men, who were diagnosed as having CAD by coronary angiography, a history of previous myocardial infarction, unstable angina, or stable angina pectoris with positive myocardial ischemia tests according to definitions used in other studies.[25-27] Patients were recruited without establishing an age limit, in a non-selective and consecutive way, from among patients referred for echocardiography. We excluded patients in a terminal situation due to uncontrolled heart failure, serious intercurrent infections, or advanced kidney failure, as well as patients for which no clinical history of risk factors or treatment was available.

A survey was used to collect the risk factors, which included male sex or menopause, age, smoking habit, arterial hypertension, diabetes mellitus, hypercholesterolemia, family history of premature coronary artery disease (men<55 years or women<65 years), and obesity (30 BMI>kg/m^2). We confirmed the treatment followed for at least the 7 days before the test was carried out because the aim of the study was to confirm the influence of pharmacological measures on the grade of endothelial function. For that reason, 416 patients who were being treated with drugs from two or more different groups were excluded. Later, patients were classified into 5 groups according to treatment: group A included 81 control patients treated with aspirin or another platelet antiaggregant and general health measures recommended for coronary patients; group B was constituted by 198 patients treated with ACEIs; group C included 106 patients who received calcium antagonists; group D included 145 patients using beta-blockers, and group E was formed by 135 patients, 93% of which were treated with lipid-lowering, HMG-CoA reductase inhibitors (statins).

Study of flow-mediated dilation

The studies were made in the morning, while fasting, under stable temperature conditions, with the patient lying down and at rest for at least 10 min, without discontinuing the medication being used. Endothelial function was evaluated using a previously validated technique.[23,24,28,29] The brachial artery was visualized with a 9.5-MHz high-resolution transducer using a Sonotron VingMed CMF800 echograph. In all patients, a fairly straight segment of artery was identified in the right antecubital fossa and its location was marked. After optimizing image depth and gain, baseline images were obtained. We then inflated a pressure cuff placed at least 3 cm above the analysis point to 60 mm Hg above systolic blood pressure and kept it inflated for 3 min. We obtained the immediate percentage increase in the velocity of hyperemic flow and the images of the brachial artery one minute after decompressing the cuff. Ten minutes after recovering baseline diameter, 200 µg of sublingual nitroglycerin was administered and the diameter the brachial artery was

measured in 3 min. The mean value of 5 determinations was calculated. The FMD was used as an index of dilation dependent on the endothelium and nitroglycerin-mediated dilation (NMD) reflected the independent dilation of the endothelium. The diameter of the brachial artery was measured coinciding with the R wave of the ECG. In our laboratory, the variability for determinations of brachial artery diameter was 0.09±0.06% intraobserver and 0.13±0.08% interobserver, and the variability for FMD was 2.8±1.54% intraobserver.

Laboratory study

In the 2 weeks before or after inclusion, the lipid profile (total cholesterol, triglycerides, HDL-C, and LDL-C) and blood glucose were analyzed.

Statistical analysis

The variables were described as mean±SD for continuous numerical values and as proportions for categorical values. The differences between independent therapeutic groups for non-categorical variables were analyzed by analysis of variance (one-way ANOVA), and the difference of proportions for categorical variables, by χ^2. Multivariate analysis was carried out according to logistic regression to find independent predictors of categorical variables, and by stepwise multiple linear regression for continuous numerical variables. A value of $P<.05$ was considered statistically significant.

RESULTS

Characteristics of patients

Chronic CAD was observed in 447 patients (67.2%), of which 215 (32.3%) had been diagnosed as old myocardial infarction, 71 (10.7%) had coronary revascularization by coronary bypass, 139 (20.9%) had undergone percutaneous angioplasty, and 124 (18.6%) had stable chronic angina (Table 1). Two hundred and eighteen (32.8%) presented acute CAD of less than 2 weeks of evolution, 108 (16.2%) had unstable angina, 36 (5.4%) non-Q-wave infarction, and 79 (11.9%) acute Q-wave myocardial infarction. Forty-five patients (6.8%) had cerebrovascular accident and 29 (4.4%) had peripheral vascular atherosclerotic disease. The differences between groups are shown in Table 1. Compared with the control group, patients with old myocardial infarction were often treat with ACEIs or calcium antagonists ($P<.05$), patients undergoing percutaneous revascularization were treated more frequently with calcium antagonists ($P<.05$), and patients diagnosed as stable angina were usually treated with calcium antagonists, beta-blockers, and lipid-lowering agents ($P<.05$). In patients with unstable angina, treatment with beta-blockers or calcium antagonists predominated, patients with acute non-Q-wave infarction were treated mainly with calcium antagonists, and patients with acute Q-wave infarction were treated with ACEIs and beta blockers ($P<.05$).

The characteristics of each therapeutic group and the overall group with respect to patients´ risk profiles are shown in Table 2. The patients who received pharmacological treatment, especially in the ACEI, calcium antagonist, or statin treatment groups, were older, more frequently women, diabetics, dyslipidemic, hypertensive, and had less favorable lipid profiles.

The drugs included in each group and the doses are presented in Table 3.

Analysis of endothelial function. Differences between groups

We found that the FMD was higher in all the treatment groups than in group A This difference was significant only in the ACEI group (3.42±6.01 versus 0.82±6,04; $P<.05$) and was almost statistically significant in the group with lipid-lowering treatment (2.08±5.28 versus 0.82±6,04; $P=.08$). In groups with

Table 1. **Differences in atherosclerotic complications, by type of treatment**

	Group A	Group B	Group C	Group D	Group E	Total
Old infarction	32.1% (26)	43.4%* (86)	45.3%* (48)	22.1% (32)	17.0% (23)	32.3% (215)
Bypass	16.0% (13)	9.6% (19)	4.7% (5)	6.2% (9)	17.8% (24)	10.7% (71)
Angioplasty	22.2% (18)	17.75% (35)	28.3%* (30)	14.5% (21)	25.9% (35)	20.9% (139)
Stable angina	7.4% (6)	12.6% (25)	26.4%* (28)	26.9%* (39)	19.3%* (26)	18.6% (124)
Acute Q-wave infarction	11.1% (9)	14.6%* (29)	3.8%* (4)	17.2%* (25)	8.9% (12)	11.9% (79)
Acute non-Q-wave infarction	6.2% (5)	3.0% (6)	11.3%* (12)	4.8% (7)	4.4% (6)	5.4% (36)
Unstable angina	7.4% (6)	10.1% (20)	20.8%* (22)	32.4%* (47)	9.6% (13)	16.2% (108)
No. of previous coronary events per patient	1.02	1.11	1.41	1.24	1.03	1.16
Cerebrovascular accident	7.4% (6)	8.0% (16)	6.6% (7)	3.4% (5)	8.1% (11)	6.8% (45)
Peripheral vascular disease	3.7% (3)	5.0% (10)	6.6% (7)	1.4% (2)	5.2% (7)	4.4% (29)

* $P<.05$ versus group A (ANOVA).

Table 2. **Differences in the profile of risk factors, by type of treatment**

	Group A (n=81)	Group B (n=198)	Group C (n=106)	Group D (n=145)	Group E (n=135)	Total (n=665)
Age, years	52.5±12.5	65.1±11.2[a]	66.9±11.1[a]	64.9±14.2[a]	62.5±11.8[a]	68±12
Mode	54	66	68	63	63	66
Range	25-84	32-87	29-91	26-89	27-88	25-91
Female sex	22.2%[b]	26.3%	28.3%	27.6%	29.6%	27.1%
Diabetes mellitus	12.3%	36.4%[a]	24.5%[a]	19.3%	27.4%[a]	26.0%
Arterial hypertension	17.3%	57.9%[a]	54.4%[a]	37.2%	43.7%[a]	45.0%
Dyslipidemia	25.9%	26.8%	37.7%[a]	25.5%	68.1%[a]	36.5%
Smoker	45.7%[a]	18.2%	16.0%	23.4%	25.9%	23.9%
Ex-smoker	16.8%	31.9%[a]	37.5%[a]	23.7%	43.7%[a]	31.6%
Familial history	22.2%	25.3%	19.8%	11.0%[a]	31.1%[a]	22.1%
Systolic blood pressure	136±21	149±22[a]	150±23[a]	138±25	135±22	139±24
Diastolic blood pressure	86±13	903+13[a]	88±10[a]	84±12	86±12	87±13
Glucose, mg/dL	114.7±33.7	123.4±32.2[a]	106.9±23.4	111.3±32.0	113.9±36.5	113.1±29.6
Total cholesterol, mg/dL	205±41	223±36[a]	219±42[a]	206±38	235±45[a]	219±41
Triglycerides, mg/dL	128±78	151±137[a]	140±72	138±72	146±56[a]	143±81
LDL, mg/dL	128.5±32.2	145.0±33.5[a]	139.1±43.2	129.2±3.6	157.8±5.3[a]	141.1±35.4
HDL-C, mg/dL	45.7±12.5	43.4±12.2	55.4±16.6[a]	46.0±11.8	44.6±11.5	46.4±12.4
BMI, kg/m^2	25.8±3.4	27.9±3.5[a]	28.0±4.0[a]	27.3±4.0	28.9±3.2[a]	27.4±3.7
No. of risk factors	2.14±0.89	2.74±0.79[a]	2.35±0.75	2.17±0.91	3.45±0.70[a]	2.57±0.81

[a]*P*<.05 versus group A (ANOVA). [b]*P*<.05 versus groups B-E. (ANOVA).
LDL-C indicates cholesterol bound to low-density lipoproteins; HDL-C, cholesterol bound to high-density lipoproteins; BMI, body mass index; No. of risk factors, male sex or menopause, age, active smoking habit, ex-smoker<10 years, or smoker more than 10 years, arterial hypertension, diabetes mellitus, hypercholesterolemia, family history of premature coronary disease (men<55 years or women<65 years), and obesity (30 BMI>kg/m^2).

Table 3. **Drugs included in each therapeutic group and dose used (therapeutic interval and mean)**

ACEI
- Enalapril (5-40 mg/day, 17.7±5.1)
- Cilazapril (2.5-10 mg/day, 4.6±1.1)
- Captopril (12.5-150 mg/day, 68.5±21.3)
- Ramipril (2,5-10 mg/day, 4.3±0.9)
- Quinapril (5-40 mg/day, 22.5±6.2)

Calcium channel antagonists
- Diltiazem (120-360 mg/day, 212.2±30.5)
- Amlodipine (5-20 mg/day, 6.9±0.8)
- Nifedipine (10-60 mg/day, 33.8±7.1)

Beta-blockers
- Atenolol (25-150 mg/day, 55.2±10.2)
- Carvedilol (6.25-75 mg/day, 21.8±6.8)
- Bisoprolol (2.5-10 mg/day, 5.1±0.8)

Lipid-lowering drugs (statins, fibrates)
- Simvastatin (10-40 mg/day, 13.6±1.4)
- Pravastatin (10-40 mg/day, 16.3±2.1)
- Fluvastatin (10-40 mg/day, 19.3±3.7)
- Lovastatin (10-40 mg/day, 18.8±3.4)
- Atorvastatin (10-40 mg/day, 12.3±1.1)
- Cerivastatin (0,1-0,4 mg/day, 0.27±0.09)
- Gemfibrozil (300-1800 mg/day, 786±91)

calcium antagonists and beta-blockers, the differences were not significant (*P*>.10). The independent dilation of the endothelium (NMD) did not differ significantly between groups. The diameter of the brachial artery and increased flow rate were greater in all the treatment groups versus the control group, and the flow rate was also higher in the groups treated with calcium antagonists and beta-blockers versus those treated with ACEIs or statins (Table 4).

Although FMD is a continuous variable and any cutoff point is artificial, for practical purposes we proposed to find a cutoff point related with greater coronary risk. This, in theory, would constitute a prevention goal. Until present, the Framingham risk scale, obtained as a score using the profile of risk factors, is the best way to quantify coronary risk in non-atherosclerotic patients.[17] Our group[30,31] had analyzed a broad sample of non-coronary patients with different risk factors, finding a significant correlation between the Framingham scale and FMD, which suggested the validity of FMD as a cardiovascular risk index. According to the Framingham tables, a score over 21 points corresponds to a coronary risk ≥20% at 10 years, which was considered moderate-to-high (equivalent to that of a stable coronary patient).[17,32] This was extrapolated to an FMD of 4% (Figure 1) and it seemed logical to use this value as a cutoff point for coronary risk. Another argument in favor of establishing this cutoff point was that other groups, such as that of Schroeder et al.,[33] found a similar FMD value, <4.5%, that is predictive of CAD in patients with a clinical suspicion of this condition referred for coronariography. When the percentage of patients who obtained a FMD>4% was analyzed, we found that group B

Table 4. **Differences in parameters related to flow-mediated dilation, by treatment**

	Group A	Group B	Group C	Group D	Group E
FMD	0.82±6.04	3.42±6.01[a]	1.75±5.51	1.21±5.44	2.08±5.28[a]
NMD	7.9±1.1	8.3±1.5	8.2±1.4	7.5±1.6	8.1±1.3
Brachial diam.	3.51±0.65	3.92±0.69[a]	4.10±0.71[a]	4.04±0.69[a]	3.88±0.62[a]
Δ flow velocity	107±59	166±124[a]	214±199[a,b]	228±215[a,b]	148±126[a]

[a]*P*<.05 versus Group A (ANOVA). [b]*P*<.05 versus groups B and E (ANOVA).
Brachial diam. indicates diameter of brachial artery; Δ flow velocity, increase in flow velocity with hyperemia; FMD, flow-mediated dilation; NMD, nitroglycerin-mediated dilation.

Table 5. **Data collected by multiple linear regression analyses of the independent predictors of grade of flow-mediated dilation**

Variables of model	Non-standardized coefficients (B)	Standardized coefficients (β))	*P*
(Constant)	10 323		.007
Age	−0.128	−0.208	.001
Smoking	−2.874	−0.124	.021
AHT	−2.151	−0.133	.015
Female sex	3.564	0.222	.015
Menopause	−5.802	−0.359	.000
Dyslipidemia	−0.909	−0.055	.339
Diabetes	−0.404	−0.045	.385
BMI	0.0135	−0.016	.748
ACEI	2.565	0.116	.039
Statins	3.452	0.167	.010
Calcium antagonists	−0.517	0.021	.708
Beta-blockers	−1.693	−0.080	.173

AHT indicates arterial hypertension; BMI, body mass index.

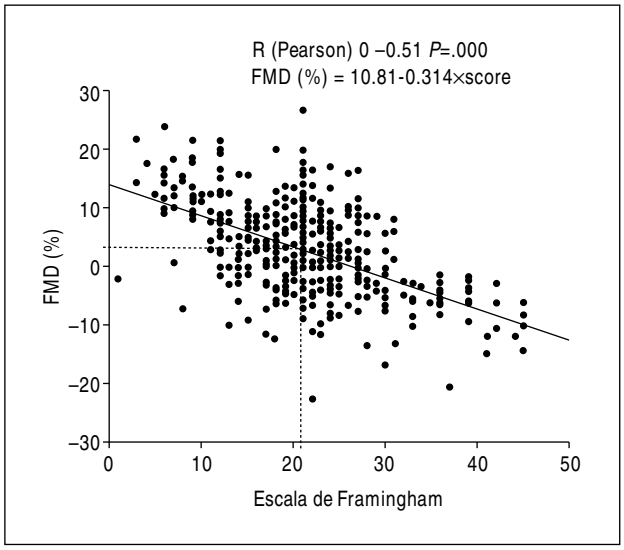

Fig. 1. Correlation of the Framingham risk scale and FMD. The grade of endothelial function assessed by FMD (%) that is equivalent to a coronary risk at 10 years of more than 20% (score≥21) is approximately 4%.

(n=98; 49.5%) and group E (n=48; 35.6%) significantly surpassed the objective compared to group A (n=15; 18.5%; *P*<.05), in contrast with the patients in groups C (n=30; 28.3%) and D (n=39; 26.9%) (*P*>.05) (Figure 2).

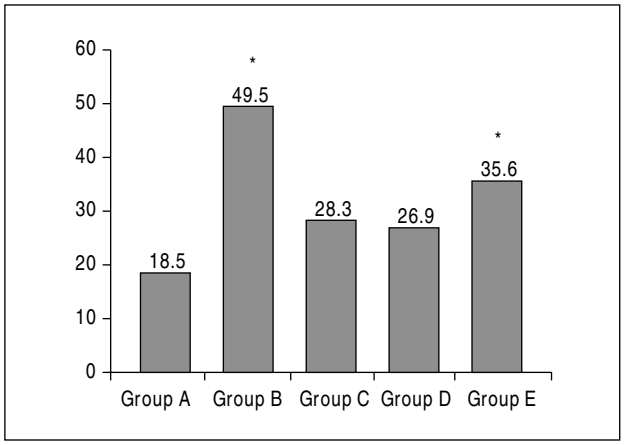

Fig. 2. Percentage of patients who reach the prevention goal of FMD>4%. *P<.05 versus group A.

Independent predictors of grade of endothelial dysfunction

We analyzed the predictors of FMD grade by multiple linear regression, and included treatment in the analysis model, as well as the profile of risk factors that undoubtedly influenced the grade of endothelial function (Table 5). We found that treatment with ACEIs (β=0.116; *P*=.039) and statins (β=0.167; *P*=.010) were independent predictors of the grade of endothelial function. By multiple logistic regression, we analyzed predictors of FMD>4%, including the same variables as in the previous model (Table 6). Treatment with ACEIs increased the probability of normalizing endothelial function (FMD>4%) by 63.21% (odds ratio [OR]=1.63; 95% CI, 1.13-3.4; *P*=.0145), and with lipid-lowering agents, by 189.27% (OR=2.89; 95% CI, 1.28-6.55; *P*=.0109). Other independent predictors of the grade of endothelial function were age (β=–0.208; *P*=.01), smoking habit (β=–0.124; *P*=.021),

Table 6. **Multivariate analysis of logistical regression. Predictors of risk of improving flow-mediated dilation by more than 4%**

Variables of model	*P*	RR	95% CI for relative risk	
			Lower	Higher
Male sex	.5643	0.7580	0.2955	1.9443
Age	.0003	0.9544	0.9306	0.9788
Menopause	.6059	0.7708	0.2867	2.0720
Dyslipidemia	.9595	0.9850	0.5483	1.7692
Smoker	.1008	0.5265	0.2447	1.1328
Diabetes	.8252	0.7749	0.5810	1.0334
AHT	.0699	0.6116	0.3594	1.0409
Family history	.5756	0.8733	0.5434	1.4034
BMI	.3946	0.9797	0.9345	1.0271
Beta-blockers	.1957	0.7649	0.1626	1.3191
Calcium antagonists	.9327	1.0366	0.4505	2.3851
ACEI	.0145	1.6321	1.1271	3.4280
Statins	.0109	2.8927	1.2769	6.5529
Constant	.022	4.2697	1.3974	9.3365

IC indicates confidence interval; RR, relative risk; AHT, arterial hypertension; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitors.

arterial hypertension (β=–0.133; *P*=.015), female sex (β=0.222; *P*=.015), and menopause (β=–0.359; *P*=.000). Nevertheless, only age (OR=0.95; 95% CI, 0.9306-0.9788; *P*=.0003), and the treatments indicated, were independent predictors of a FMD>4%.

DISCUSSION

Knowledge of the status of endothelial function could be an interesting asset in the treatment of coronary patients in clinical practice. Invasive techniques that assess vasodilator response to acetylcholine are used.[5,6] Alternative techniques have been proposed to assess peripheral arterial vasodilation using stimuli like hyperemic shear stress or cold, which are assumed to be mediated by the endothelium. This assumption is based on the changes demonstrated in situations of cardiovascular risk and their correlation with measurements obtained by invasive techniques.[24] Nevertheless, we do not know what mechanisms mediate FMD and whether they truly measure the state of the endothelium. Calcium-activated potassium channels open in response to shear stress by hyperpolarizing the endothelial cell and activating endothelial nitric oxide synthase (eNOS) in response to calcium.[34-36] In rats with an eNOS deficit, FMD is kept normal by prostanoids derived from the endothelium and is modified by indomethacin.[37] Given the ample literature that characterizes FMD as dependent on the endothelium, we decided to use this method to examine the state of endothelial function.

Comments on results

Our findings with regard to the effect of treatment on FMD are compatible with findings reported in the literature. The neutral effect of calcium antagonists on endothelial function confirms the results of the BANFF study[38] and could explain why calcium antagonists, at the usual dose, fail to reduce coronary events although they apparently detain the progression of atherosclerosis.[39-41] Although beta-blockers seem to improve endothelial function by their direct antihypertensive effects,[42] alpha-adrenergic blockade,[43,44] antioxidant effects, or direct improvement of eNOS function,[45] the findings are still contradictory and insufficient.[46] In our case, no clear effect on FMD is confirmed. Independently of its effects on FMD, at present the preventive action of beta-blockers is unquestionable in relation to independent mechanisms of its effect on endothelial function.

ACEIs have been shown to produce clear benefits on endothelial function,[21,38] as well as a reduction in coronary events.[20] In contrast with the BANFF study, although we did not make a differential analysis of the various ACEIs, the favorable effect seems to occur in generally in the group. Nonetheless, the reported results of the action of ACEIs on endothelial function have been disparate. It is possible that this effect depends on the liposolubility of the ACEIs, originating different types of tissular ACE blockade.[21,38] Our results suggest that in the heterogeneous overall population of patients with CAD, ACEIs as a group produce beneficial effects on FMD. This would concur with the presence of favorable clinical results in randomized trials of different ACEIs in patients with previous myocardial infarction.[47,48]

Lipid-lowering agents, mainly statins, have been widely shown[18,19] to improve the prognosis of coronary patients, and constitute the keystone of secondary prevention measures. They have demonstrated a normalizing effect on endothelial function in patients with hypercholesterolemia,[49,50] and coronary artery disease with or without hypercholesterolemia.[51] A recent study of pravastatin (RECIFE)[22] in acute coronary patients has demonstrated a short-term benefit on FMD that parallels the effect on lipids, hemostatic factors, and endothelin concentrations. Likewise, it concurs with the beneficial effects found in patients who receive early treatment with high doses of statins[52] after presenting an acute coronary syndrome. Almost one third of our patients presented acute CAD of less than 2 weeks duration and, in contrast with the RECIFE study, which evaluated FMD at 6 weeks, we found an earlier beneficial effect with ACEIs or statins, independent of their later antihypertensive or lipid-lowering effects. In univariate analysis, the statins had a less potent nor-

malizing effect on FMD than the ACEIs. After adjustment for other variables, lipid-lowering treatment had an independent beneficial effect. We know, from the findings of the JADE study, that in Spain only 14.7% of coronary patients present suitable LDL concentrations.[53] There is little indication for lipid-lowering drugs and when their administration begins, therapeutic objectives are rarely reached. Our data indicate that total cholesterol (235 mg/dL) and LDL (158 mg/dL) concentrations in the group that received lipid-lowering treatment were higher than in the other groups. The results of the CARE trial[18] and LIPID trial[19] indicate that to obtain a significant decrease in cardiovascular risk we must initiate statin treatment at LDL values of 130 mg/dL. Aside from these parameters, which have been generally adopted by all secondary prevention programs,[32,54,55] we have no other instruments to guide preventive measures. An advance in optimizing preventive measures would be an approach to assessing individual risk by evaluating endothelial function.

Study limitations

Endothelial dysfunction has been related to the CAD development and would be a logical parameter to guide preventive measures. Nevertheless, although recent small studies seem to confirm that coronary endothelial dysfunction assessed by invasive techniques can constitute a predictor of cardiovascular complications,[15,16] at present there are no data that confirm that peripheral endothelial dysfunction, assessed as FMD, is a risk indicator. We cannot conclude that a treatment that improves FMD predicts a better prognosis until knowing the results of studies under way that confirm the prognostic value of this parameter.

Another limitation that we encountered is the necessary heterogeneity of any broad sample of coronary patients, which show differences in the intensity of atherosclerotic disease and the risk profile, thus limiting comparisons between groups. In order to compare the differences in FMD with treatment, the baseline situation must be known. Nevertheless, our study only proposes to know the result of therapeutic measures initiated by cardiologists on FMD in clinical practice. Given the wide range of drugs used in practice and the clinical heterogeneity of the coronary patient, we needed a very large sample of patients. It is ethically impossible to discontinue physician-prescribed treatment to assess baseline FMD and then reinitiate it. We know that, overall, coronary patients have an endothelial dysfunction of similar grade, independent of the clinical situation of the patient. In fact, patients with coronary atherosclerosis and patients with angina without coronary lesions have similar grades of endothelial dysfunction.[56] In addition, we corrected this bias by means of multivariate analysis, adjusting the effect of treatment for the profile of risk factors, which does seem to be related to the grade of baseline endothelial dysfunction.[31] For that reason, we believe that these methodological limitations only partially curtail the validity, but never the interest, of our results. In addition, patients under pharmacological treatment, especially with ACEIs, calcium antagonists, and statins presented a greater number of previous cardiac events and a more adverse profile of risk factors than the control group, which would confirm even more its beneficial effect. Although the effect of ACEI on endothelial function in univariate analysis was greater than that of treatment with statins, and clearly superior to the other two treatment groups and the control group, when the effect was adjusted for the level of risk, the benefit attributable to ACEI treatment existed, but was less than the benefit obtained with lipid-lowering therapy. Finally, the vasodilator stimulus is the increase in flow velocity, which was greater in patients treated with beta-blockers or calcium antagonists, which is yet another confirmation of the differences in FMD in favor of the ACEIs and statins.

Another limitation is the variability in FMD results. The FMD and NMD values in our sample can reveal differences in absolute value compared with the values reported by other authors. This can be explained by differences in the ischemic interval of 3-5 min, the nitroglycerin doses administered (200-800 μg), and the time to image collection after hyperemia or nitroglycerin[57] according to some studies. In addition, patient samples can be heterogeneous between publications and most include patients at lower risk than our population. This variability explains the absence of cutoff points for judging the FMD as pathological, which is why we derived a cutoff value of 4% based on previous experience.[31] In addition, this has led recently to the introduction of guidelines for calculating a cutoff value for the purpose of obtaining uniform results.[29]

Contributions of the study

We have confirmed the possibility of applying a technique for evaluating the state of endothelial function in clinical practice. Although the present findings do not confirm the prognostic value of FMD, in the future it could be an instrument for the follow-up of coronary patients. In this case, our findings were useful in monitoring the effect of the therapies used.

CONCLUSION

FMD analysis is a feasible monitoring technique in the follow-up of coronary patients. Despite the limitations discussed, ACEI and statin treatment were the pharmacological measure that most normalized FMD in clinical practice in coronary patients.

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