Implications of Late Expansion of Self-Expanding Stents on Neointimal Response: a Serial Study with Intravascular Ultrasound

Marcelo Sanmartín, Javier Goicolea, Fernando Alfonso, Javier Escaned, Álex Flores, Antonio Fernández-Ortiz, Camino Bañuelos, Rosa Ana Hernández-Antolín and Carlos Macaya

Servicio de Cardiología Intervencionista. Instituto Cardiovascular. Hospital Clínico San Carlos. Madrid.

Introduction and objectives. A unique property of self-expanding stents is the continuous force exerted against the vessel wall, which may induce additional arterial damage with implications on restenosis. The main purpose of this study is to evaluate the consequences of late self-expansion of coronary Wallstents.

Methods. Eleven patients with Wallstents implanted in native coronary arteries, in whom baseline, post-stenting, after high pressure balloon inflation and at 6-month follow-up intravascular ultrasound were performed. The stented segments were divided in 2-mm cross-sections, that were analyzed independently and carefully matched at each situation using anatomic landmarks. Multiple regression analysis was performed.

Results. Late expansion was present in 93% of the studied sections (mean increase in stent area of 2.0 ± 1.9 mm^2) and was clearly related to stent oversizing (r = .45; P < .0001). Although late expansion was a significant positive predictor of neointimal growth (r = .63; P < .0001), it showed a negative correlation with late luminal loss (r = –.33; P < .0001). No significant correlation was found between optimization of angiographic results with high pressure inflations and late luminal loss.

Conclusions. Late expansion is a common phenomenon after Wallstent implantation and is mainly determined by stent oversizing. Despite the fact that this phenomenon is associated with greater neointimal proliferation, it seems to have a net beneficial effect on late luminal loss.

Key words: *Stents. Restenosis. Coronary angioplasty.*

Implicaciones de la expansión tardía de los stents autoexpansibles sobre la respuesta neointimal: estudio seriado con ecografía intravascular

Introducción y objetivos. La presión continua ejercida por los *stents* autoexpansibles contra la pared arterial podría tener implicaciones sobre la reestenosis. El objetivo principal de este estudio es evaluar las consecuencias de la autoexpansión del Wallstent en arterias coronarias.

Métodos. Se evaluaron 11 pacientes con Wallstents implantados en arterias coronarias nativas en los que se realizó una ecografía intravascular en situación basal, tras la liberación del *stent*, tras inflados con balón a altas presiones y a los 6 meses. Los segmentos tratados fueron divididos en secciones a intervalos de 2 mm, que fueron analizados de forma independiente y emparejadas mediante marcadores anatómicos. Las variables de estudio fueron sometidas a un análisis de regresión múltiple.

Resultados. La expansión tardía ocurrió en el 93% de las secciones estudiadas (incremento medio en el área del *stent* de 2,0 ± 1,9 mm^2) y tenía una relación positiva con la sobredimensión del *stent* (r = 0,45; p < 0,0001). La expansión tardía era un determinante positivo independiente de crecimiento neointimal (r = 0,63; p < 0,0001), aunque exhibía una correlación negativa con la pérdida luminal tardía (r = –0,33; p < 0,0001). No se encontró correlación significativa entre la optimización de la angioplastia con inflados a alta presión y la pérdida luminal tardía.

Conclusiones. La expansión tardía es común tras la implantación de Wallstents y está fundamentalmente relacionada a la sobredimensión del *stent*. Dicho fenómeno parece inducir mayor proliferación neointimal pero, al producir también un incremento tardío en el área total del vaso, el efecto neto sobre la luz parece beneficioso.

Palabras clave: Stents*. Reestenosis. Angioplastia coronaria*.**I**

INTRODUCTION

Stents have become almost routine in current percutaneous coronary interventions since it was demonstrated that restenosis rates are lower in several angiographic subgroups.[1-7] Information obtained by

Correspondencia: Dr. M. Sanmartín.
Unidad de Cardiología Intervencionista.
Hospital Meixoeiro, apto. oficial s/n. Vigo. 36200 Pontevedra. Sapin
Correo electrónico: msanmartin@teleline.es

Received 28 February 2001
Accepted for publication 19 June 2001

ATABLE OF ABBREVIATIONS

IVE: intravascular echography
LE: late expansion
OEL: outer elastic layer
LA: luminal area
SA: stent area
PBLG: post-balloon luminal gain
OI: oversizing index

intravascular echography (IVE) has allowed new and simpler antithrombotic guidelines to be used and has given us a better understanding of the mechanisms of luminal reduction after angioplasty.[8-12] However, these observations for the most part have been made with a specific type of stent (Palmaz-Schatz) and may not be applicable to other stent designs,[13,14] particularly self-expanding stents like the Wallstent.

The Wallstent was designed in the 1980s as a complementary device to balloon angioplasty, particularly for the treatment of threatened vessel closure.[15-20] Continuous expansion, a singular property of this type of stent, could have implications for late results because it originates dynamic interactions with the arterial wall in addition to the presence of the metal mesh foreign body. Studies with quantitative angiography have demonstrated that a certain degree of late expansion (LE) occurs and it has been suggested that this could increase neointimal proliferation.[21] Nonetheless, the determinants of LE and its final implications have not been appropriately evaluated. The objective of this study is to analyze the mechanisms of neointimal response and luminal loss after Wallstent implantation in coronaries using information obtained by IVE.

METHODS

Patients

The study group was formed by 11 consecutive patients with at least one Wallstent (Schneider, Bülach, Switzerland) implanted in a native coronary artery and an IVE study of adequate quality carried out at each of the following timepoints: *1)* before stent implantation; *2)* immediately after stent release; *3)* after optimizing results with high-pressure balloon inflation, and *4)* 6 months after angioplasty. Informed consent was obtained for the procedure in every case.

Stent implantation

Angioplasty was performed via the femoral path in every patient using 8-Fr introducers and 8-Fr guide catheters. All patients were given aspirin and 10,000 units of heparin before the procedure. In every case the stenosis was predilated non-aggressively using balloons with nominal diameters 0.5 to 1 mm smaller than the angiographic reference diameter to facilitate the insertion of the stent in the damaged segment. After predilation and intracoronary nitroglycerin, the first IVE study was performed using 30-MHz catheters (UltraCross 3.2 Fr, Scimed, Maple Grove, MN, USA). The Wallstents inserted were selected in accordance with the angiographic assessment of the distal and proximal reference diameters and the length of the lesion. They had a nominal diameter at least 1.0 mm larger than the maximum reference diameter. Balloon dilation was performed after stent implantation to correctly expand it, following the angiographic and IVE criteria in the published MUSIC trial.[22] A final echographic study was made before the guide catheter was removed.

After angioplasty, patients were treated with a combination of aspirin and ticlopidine. A new coronary angiography and IVE study were made 6 months later.

IVE studies

In every case, IVE was performed before and after stent release, after balloon inflation, and at 6 months of follow-up. The IVE catheters were introduced after an intracoronary injection of nitroglycerin (a 200-mcg bolus). Images were acquired on standard VHS tapes during continuous automatic removal at 0.5 mm/s. The IVE images were divided into 2-mm sections for paired comparisons between studies. The sections were digitalized and processed on a computer system specially designed for this purpose and described in earlier studies.[23] In summary, the video recordings were reproduced on the monitor of a personal computer and selected sections were archived as individual files. This method enabled simultaneous review of several sections and morphometric analysis with specialized software (NIH Image, v. 1.61, National Institutes of Health, Bethesda, USA). In this study, anatomic markers were used to pair the images taken in different temporal situations before and after stent implantation. Since it is assumed that stent length shortens considerably after balloon dilation and over time, the stent margins were not used as markers.

TABLE 1. **Clinical, angiographic, and intravascular echography data**

Age (years)	55.6 ± 10.9
Women	1 (9%)
Previous MI	1 (9%)
Unstable angina	10 (91%)
Risk factors:	
Hypertension	4 (36%)
Diabetes	3 (27%)
Dyslipidemia	8 (73%)
Smoking habit	6 (55%)
Angiographic variables:	
Treated coronary artery	
AD	5 (46%)
RC	4 (36%)
CX	2 (18%)
Stenosis (%)	84.5 ± 9.3
Reference diameter (mm)	3.6 ± 0.4
Pre-intervention MLD (mm)	0.5 ± 0.2
Post-intervention MLD (mm)	3.2 ± 0.2
IVE variables*	
OEL (mm2)	13.1 ± 4.0
LA (mm2)	5.3 ± 2.8
Plaque area (mm2)	7.8 ± 3.7
Calcification arc	30.7º ± 66.2
Disease-free arc	36.7º ± 5.7
Score	5.7 ± 2.5
Oversizing index	1.40 ± 0.58

MI = myocardial infarction; AD = anterior descending; RC: right coronary artery; CX: circumflex; MLD = minimal luminal diameter; IVE = intravascular echography; OEL = outer elastic layer; LA = luminal area.
*IVE calculations are detailed in the text.

Consequently, the time interval between the distal edge of the stent at its longest length (the first IVE obtained after stent release) and the coronary ostium or another fixed marker like a lateral branch was used. This time interval was used to locate the same point on other IVE recordings. As an additional measure to ensure precision, two or three sections with characteristic markers, such as the presence of lateral branches or deep calcification, were visualized simultaneously on the monitor to carry out the necessary adjustments for pairing. One researcher (MS) managed the images and made all measurements.

IVE variables

A total of 166 of sections were analyzed. In each situation the areas of the outer elastic layer (OEL), lumen (LA), and stent (SA) were measured. The calcium arc and «disease-free arc» were taken from the baseline IVE. Plaque area referred to the area of the plaque + media and was calculated by «OEL – LA,» late luminal loss was calculated as «post-procedure LA – 6-month LA», and LE was calculated by «6-month SA – post-procedure SA.» In every case, a strategy of aggressive balloon dilation was followed using predefined echographic criteria.[22] To evaluate the effects of this strategy, the change in SA was measured between the IVE made after stent release and the final IVE of the procedure. The increase in SA secondary to inflation was designated post-balloon luminal gain (PBLG).

The effects of the radial pressure produced by stent self-expansion were evaluated using a specific index (the oversizing index, or OI), which was calculated using the OEL obtained in each section of the baseline IVE and the manufacturer's nominal stent area (OI = nominal stent area/baseline OEL).

Other variables measured were compared with plaque characteristics, such as the area of the plaque, presence or absence of calcification, and a point score obtained using a scale designed by our group. This score was determined from the arithmetic sum of the points assigned to each of 4 quadrants: 0 = absence of plaque in < 50% of the quadrant; 1 = «soft» plaque with an echographic density less than that of the adventitia; 2 = «hard» or «fibrous» plaque with a density similar to or greater than that of the adventitia; and 3 = calcified plaque.

Statistical analysis

The correlation study between echographic variables was made using the echographic sections as independent sections. The continuous variables were expressed as mean ± standard deviation. Linear regression was used to analyze the association between variables. The correlations that yielded values of $P > .15$ in the univariate model were introduced in the multiple regression model. A value of $P < .05$ was considered statistically significant. The statistical calculations were made with SPSS 8.0.

RESULTS

Patients and procedural data

The baseline data of 11 patients are summarized in Table 1. In every case lesions were new and no patient had undergone a previous revascularization procedure. Angiographic and IVE data also are shown in Table 1. The OI was 1.40 ± 0.58. Three patients required a new angioplasty during the 6-

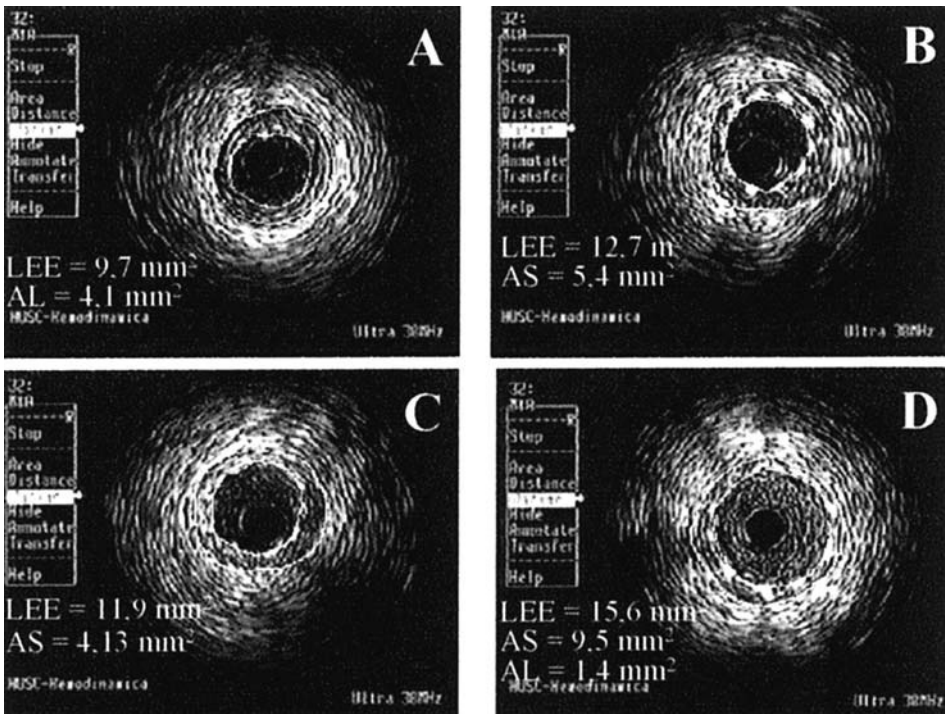

Fig. 1. Serial IVE images showing a large increase in the area of the stent from implantation (1B) to post high-pressure inflation (1C) and 6 months follow-up (1D). Figure 1 A shows the corresponding section in the baseline study. In Figure 1D, the marked neointimal proliferation that occurred in this patient is evident.
OEL indicates outer elastic layer; SA, stent area; LA, luminal area.

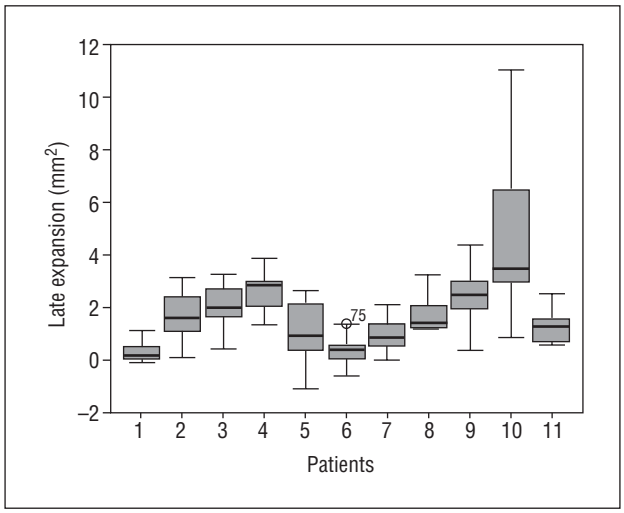

Fig. 2. Degree of late expansion in the 11 patients studied. The thick line represents the mean. The values in boxes represent the interquartile range.

TABLE 2. **Univariate correlations between echographic variables and late expansion**

	r value	Beta coefficient	95% CI	P
Calcification arc	0.4	-0.04º	-0.09/0.01	0.10
Disease-free arc	0.2	-0.005º	-0.012/0.002	0.19
Oversizing index	0.45	1.49	0.98/2.01	< 0.0001
OEL (mm2)	0.26	-0.14	-0.23/-0.05	0.003
Proximal third*	0.25	1.06	0.35/1.78	0.004
Plaque area (mm2)	0.16	0.019	-0.002/0.039	0.07
Score	0.02	-0.02	-0.16/0.13	0.82
PBLG	0.34	0.46	0.24/0.69	< 0.0001

CI, confidence interval; OEL, outer elastic layer; PBLG, post-balloon luminal gain.
*The distal third is the reference variable ("middle" is expressed as 1, middle; 0, rest and "proximal" as 1, proximal; 0, rest).

month procedure for symptomatic restenosis or silent exercise-induced ischemia.

Late stent expansion and shortening

During follow-up, 93% of the sections analyzed presented LE (Figure 1). The SA obtained in the post-angioplasty IVE and follow-up IVE increased, respectively, from 7.1 ± 1.2 mm^2 to 9.1 ± 2.1 mm^2 (P < .001). A certain degree of LE occurred in all cases, although considerable variability was observed between the coronary segments treated and the sections analyzed (Figure 2). This progressive stent expansion was associated with a significant reduction in stent length from 29.3 ± 8.7 mm to 27.2 ± 8.3 mm (P < .001). The increase in SA was significantly greater in the proximal third of the stent, with a progressive reduction in the middle and distal thirds (2.7 ± 2.9 mm^2; 2.0 ± 1.3 mm^2; 1.4 ± 1.0 mm^2; P < .01). Univariate correlations between IVE and LE variables are shown in Table 2. A note-

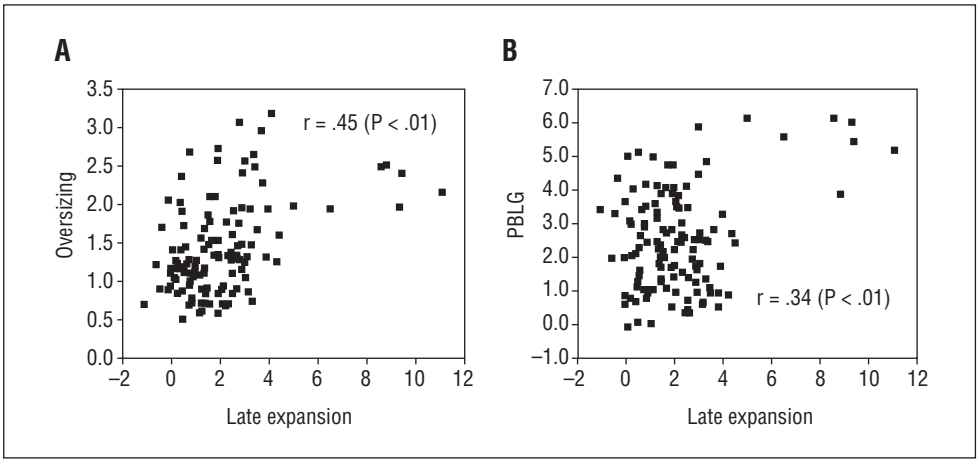

Fig. 3. Graphs of linear regression demonstrating the correlation between late expansion and stent oversizing (A) and between late expansion and post-balloon luminal gain (B).

TABLE 3. **Predictors of late expansion by multiple regression analysis (R = 0.684; R2 = 0.467)**

	Beta coefficient (adjusted)	95% CI	P
Oversizing index	1.84	1.33–2.33	< .0001
PBLG (mm2)	0.48	0.28–0.68	< .0001
*Proximal third	1.59	0.91–2.28	< .001

CI, confidence interval; PBLG, post-balloon luminal gain.
*The distal third is the reference variable ("middle" is expressed as 1, middle; 0, rest and "proximal" as 1, proximal; 0, rest).

TABLE 4. **Univariate correlations between echographic variables and the neointimal area**

	r value	Beta coefficient	95% CI	P
Calcification arc	-0.28	-0.009º	-0.014/-0.003	.001
Late expansion (mm^2)	0.63	0.70	0.55/0.85	< .0001
Oversizing index	0.65	2.38	1.89/2.87	< .0001
Plaque area (mm^2)	-0.26	-0.16	-0.26/-0.06	.001
Score	-0.19	-0.18	-0.34/-0.02	.03
PBLG (mm2)	0.25	0.38	0.13/0.64	.003

CI, confidence interval; PBLG, post-balloon luminal gain.

worthy finding was that LE correlated positively with stent oversizing, as indicated by OI (r = .45; P < .0001; Figure 3a), and with the immediate gain in SA with balloon inflation, as indicated by PBLG (r = .34; P < .0001; Figure 3b). Both OI and PBLG were identified in the multivariate model as independent positive predictors of LE, as was the situation in the proximal third (adjusted beta values in Table 3).

TABLE 5. **Predictors of neointimal hyperplasia by multiple regression analysis (R = .778; R2 = .605)**

	Beta coefficient (adjusted)	95% CI	P
Oversizing index	1.94	1.33/2.56	< .0001
Late expansion (mm^2)	0.35	0.19/0.51	< .0001
PBLG (mm^2)	0.34	0.14/0.55	< .01

CI, confidence interval; PBLG, post-balloon luminal gain.

Determinants of neointimal growth

In general, the luminal area measured by IVE decreased from 7.22 ± 1.32 mm^2 after stent implantation to 4.86 ± 2.01 mm^2 at 6 months. The variables associated with the neointimal area in univariate analysis were included in multiple regression models and are shown in Table 4. Both LE and OI showed a significant positive correlation with the neointimal area (respectively, r = .63; P < .0001 y r = .65; P < .0001; graphs of linear regression in Fig. 4). In multivariate analysis, LE, OI, and GLBP were identified as independent predictors of neointimal growth (Table 5).

Effects of LE and other variables on late luminal loss

Of all the variables studied, only OI (r = 0.27; p < 0.001), LE (r = –.33; P < .0001), and the situation in the proximal third (r = –.22; P = .012) showed a significant correlation with late luminal loss. Figure 5 shows a linear regression graph between LE and luminal loss during follow-up. In multivariate analysis, late luminal loss showed an independent positi-

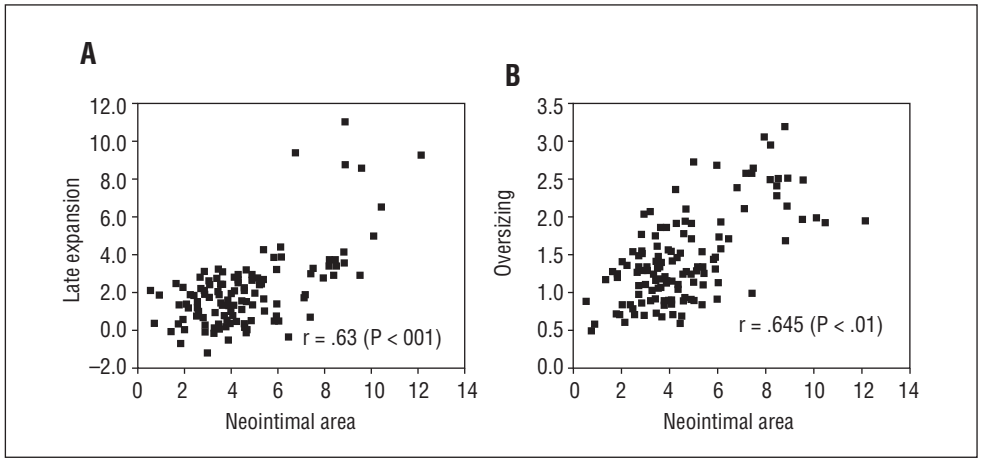

Fig. 4. Graphs of linear regression showing the correlation between the neointimal area and late expansion (A) and between neointimal area and stent oversizing (B).

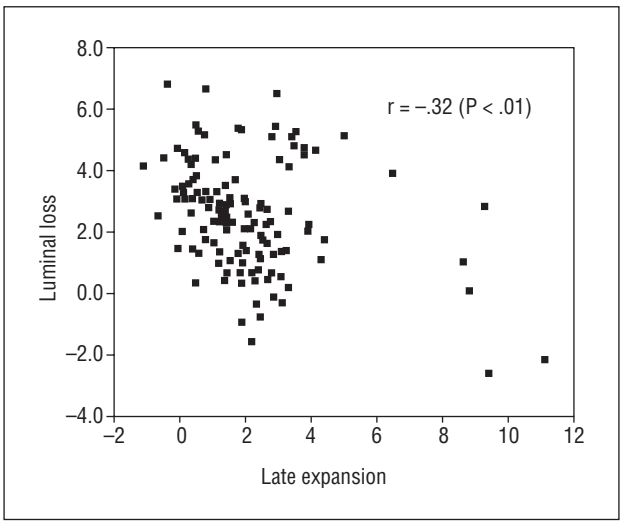

Fig. 5. Graph of linear regression demonstrating the negative correlation between late expansion and late luminal loss.

ve association with OI (adjusted beta coefficient = 1.73, 95% IC 1.21/2.24; P < .001). In spite of the positive association between LE and neointimal growth, the final effect on late luminal loss was negative (adjusted beta coefficient = –.54, 95% IC –0.70/–0.39; P < .01). Although GLBP also showed a positive correlation with the neointimal area, there was no significant association between this variable and luminal loss (r = .01; P = .8).

DISCUSSION

This study confirmed the presence of LE of the Wallstent over a period of weeks or months after the device was implanted in coronary arteries. LE appeared to be related fundamentally with the choice of stent size, rather than with the characteristics of the vessel or atherosclerotic plaque. The most relevant finding was a positive correlation between the degree of LE and neointimal proliferation, although the increase in total vessel size could compensate for luminal loss in most cases, so the final net effect was generally favorable.

The information reported by studies that include IVE[8] and the establishment of more effective antithrombotic guidelines[22,24,25] have contributed markedly to reducing complications of angioplasty with stent implantation and improving our understanding of the mechanisms of stent expansion.[26] These findings, together with the demonstration of increased restenosis with smaller post-procedure luminal areas[10-12] was the rationale for optimizing results with high-pressure inflation. Nonetheless, experimental studies on porcine models demonstrate that the degree of trauma induced by stent implantation correlates well with the degree of neointimal response.[27] Clinical investigation confirms this evidence. Hoffman et al,[28] using serial IVE images, demonstrated that neointimal thickness at 6 months is significantly greater when oversized balloons are used at higher inflation pressures (balloon/artery ratio ≥ 1.1) after implanting Palmaz-Schatz stents. Another possible source of neointimal hyperplasia may be related with irregularities in the luminal surface induced by the stent mesh or the presence of a permanent metal prosthesis with a chronic inflammatory response and continuous monocyte recruitment.[13,27-29] The incidence of restenosis also may vary with the stent model.[14] In the specific case of Wallstent self-expanding stents, the continuous radial force exerted on the arterial wall by the device could be another mechanism of chronic arterial injury and, consequently, neointimal hyperplasia. However, in the porcine model of coronary angioplasty only a weak neointimal response was observed when the

arterial wall was stretched with oversized stents, which brings this hypothesis into question.[20] In any case, it is difficult to extrapolate the findings obtained in healthy porcine arteries to a clinical context since diseased coronary arteries, which are less distensible due to the presence of hard atherosclerotic plaques, may have another type of reaction. Using quantitative angiography, von Birgelen et al[21] observed significant LE with the Wallstent in a series of 15 patients in which an oversized device was used (stent/artery ratio 1.6 ± 0.5 mm). LE occurred in spite of high-pressure inflation and correlated positively with the neointimal volume measured by IVE at 6 months. Roguin et al[31] also found a significant LE after 7-9 months follow-up with angiography in a series of patients treated with self-expanding nitinol stents (Radius). The increase in stent diameter correlated inversely with late luminal loss.[31] More recently, in another two studies using serial IVE, a positive correlation was found between LE and neointimal growth for both the Wallstent[32] and Radius stent.[33] In the present study, the IVE made before and after stent implantation and at 6 months of follow-up were used to expand these findings, and identify the main determinants of LE and establish its long-term implications.

Determinants of late expansion

LE was greatest in the most proximal segments, an effect that probably is related with larger vessel size at this level. In contrast with what was assumed, no relation was found between the characteristics of the plaque or vessel and LE. Nonetheless, given the small number of patients studied and the fact that patients with densely calcified vessels were avoided, these findings should be interpreted with reserve. As expected, the degree of stent oversizing was the main marker for LE. To evaluate the degree of oversizing, we created an index by dividing the stent area extrapolated from the nominal diameter by the vessel area obtained by IVE. We believe that this index offers more exact information about stent/artery interactions than the quantitative angiography used in previous studies.

Continuous stent expansion occurred in spite of additional enlargement of the lumen with high-pressure inflation. In fact, the luminal gain obtained with the balloon correlated positively with LE. This finding may be related to factors specific to the atherosclerotic plaque because enhanced vessel response to balloon inflation could reflect the behavior of «softer» plaques, which would be more responsive to continuous stretching induced by the Wallstent. This finding contrasts with the observation from another study that the balloon diameter used to optimize the stent area is negatively related with the degree of oversizing[21]. However, in contrast with the method used in the present study, the immediate effect of inflation on the stent area was not measured.

Late expansion, neointimal response, and luminal loss during follow-up

The main finding reported is a clear relation between LE and increased neointimal proliferation. These findings confirm previous observations and suggest that the continuous pressure that this stent model exercises on the arterial wall is a mechanism of vascular injury. The period of time over which mechanical damage occurs is not known. It cannot be assured that the stimulation of neointimal proliferation continued beyond the 6 months of follow-up, although it is likely that the interaction between the stent and the vessel reaches stabilizes within weeks or months of implantation.

In spite of acting as a stimulus to neointimal proliferation, LE seemed to suffice to accommodate excess tissue production inside the vessel, thus compensating for the late effects on luminal loss. Consequently, LE represents a form of «positive mechanical remodeling» that tends to neutralize the unfavorable effect of chronic arterial stretching. This ultimately favorable net effect on the arterial lumen confirms the findings of previous studies in this stent model[32] and other self-expanding stents with a different mesh design.[31,33]

The greater increment in the stent area obtained by balloon dilation demonstrated a positive, but relatively weak correlation with neointimal growth. Nonetheless, no correlation was found between the gain achieved with by balloon inflation and the late loss, which also suggests that enhanced proliferation was counteracted by the larger lumen achieved during angioplasty.

Study limitations

The observations were made in a small sample of patients with relatively large vessels (mean reference diameter 3.6 ± 0.4 mm) and in vessels without severe calcification, so extrapolation to other angiographic subgroups must be made cautiously. For example, the small number of cases might influence the absence of a relation between plaque characte-

ristics studied by IVE and the degree of calcification and late expansion. In addition, the analysis of cross sections of the same coronary vessel could induce error if an arbitrary repetition of a given variable or relation occurred, due to similar behavior throughout the treated segment in the same patient. However, the fact that marked inter- and intraindividual variation was observed in the degree of LE (Figure 2) suggests that the probability of this type of error is minimal for conclusions based on IVE data. In second place, a small degree of error in the pairing of sections in different echographic studies cannot be excluded. However, the method used allowed simultaneous analysis of the corresponding sections on a computer monitor, thus yielding a continuous comparison of study segments. In addition, only anatomic markers were used as reference and all measurements were made by a single investigator. This tended to minimize possible errors in the comparison of sections. Although it is known that the distal and proximal ends of a Wallstent opened extra-arterially have a larger area than the central portion, the OI calculation was made using the same area extrapolated to the entire extension of the stent. This could lead to underestimation of the radial strength of the ends of the stent, although we think that calculating a different area in the 2 or 3 sections close to the ends of the device would not greatly alter our results. Moreover, in the study of Könic et al[32], no greater degree of late expansion of neointimal growth was found at the ends (5 mm proximal and 5 mm distal) of the Wallstent compared with the middle.

CONCLUSIONS

LE is frequent after the implantation of Wallstents in coronary arteries. Although the radial force exercised by the device on the arterial wall is an added stimulus for the proliferation of neointimal tissue, the increase in overall vessel size due to LE is sufficient to accommodate the excess neointima, acting as a compensatory mechanism to produce a favorable long-term net effect on the luminal area. Finally, a more aggressive optimization of results by high-pressure inflation also contributes to stimulating neointimal formation, although the late effects counteract it.

REFERENCES

1. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G et al. A comparison of balloon expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994; 331: 489-495.
2. Fishman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I et al. A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994; 331: 496-501.
3. Sirnes PA, Golf S, Myreng Y, Molstad P, Albertsson P, Mangschau A et al. Stenting in chronic coronary occlusion (SICCO): a randomized, controlled trial of adding stent implantation after successful angioplasty. J Am Coll Cardiol 1996; 28: 1444-1451.
4. Versaci F, Gaspardone A, Tomal F, Crea F, Chiariello L, Gioffre PA. A comparison of coronary-artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. New Engl J Med 1997; 336: 817-822.
5. Savage MP, Douglas JS Jr, Fischman DL, Pepine CJ, King III SB, Werner JA et al. Stent implantation compared with balloon angioplasty for obstructed coronary bypass grafts. Saphenous Vein De Novo Trial investigators. N Engl J Med 1997; 337: 740-747.
6. Serruys PW, van Hout B, Bonnier H, Legrand V, Garcia E, Macaya C et al. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary arterry disease (Benestent II). Lancet 1998; 352: 673-681.
7. Erbel R, Haule M, Hopp HW, Franzen D, Rupprecht J, Heublein B et al. Coronary-artery stenting compared with balloon angioplasty for restenosis after initial balloon angioplasty. N Engl J Med 1998; 339: 1672-1678.
8. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 1995; 91: 1676-1688.
9. Dussaillant GR, Mintz GS, Pichard AD, Kent KM, Satler LF, Popma JJ et al. Small stent size and intimal hyperplasia contribute to restenosis: a volumetric intravascular ultrasound analysis. J Am Coll Cardiol 1995; 26: 720-724.
10. Hoffmann R, Mintz GS, Dussaillant GR, Popma JJ, Pichard AD, Satler LF et al. Patterns and mechanisms of in-stent restenosis: a serial intravascular ultrasound study. Circulation 1996; 94: 1247-1254.
11. Kasaoka S, Tobis J, Akiyama T, Reimers B, di Mario C, Wong ND et al. Angiographic and intravascular ultrasound predictors of in-stent restenosis. J Am Coll Cardiol 1998; 32: 1630-1635.
12. Werner GS, Gastmann O, Ferrari M, Scholz KH, Schunemann S, Figulla HR. Determinants of stent restenosis in chronic coronary occlusions assessed by intracoronary ultrasound. Am J Cardiol 1999; 83: 1164-1169.
13. Rogers C, Edelman ER. Endovascular stent design dictates experimental restenosis and thrombosis. Circulation 1995; 91: 2995-3001.
14. Escaned J, Goicolea J, Alfonso F, Pérez-Vizcaino MJ, Hernandez R, Fernández-Ortiz A et al. Propensity and mechanisms of restenosis in different coronary stents designs. Complementary value of the analysis of the luminal gain-loss relationship. J Am Coll Cardiol 1999; 34: 1490-1497.
15. Sigwart U, Puel J, Mirkeitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987; 316: 701-706.
16. Keane D, de Jaegere P, Serruys PW. Structural design, clinical experience, and current indications of the coronary wallstent. Cardiol Clin 1994; 12: 689-697.
17. Serruys PW, Strauss BH, Beatt KJ, Bertrand ME, Puel J, Rickards AF et al. Quantitative follow-up after placement of a self-expanding coronary stent. N Engl J Med 1991; 324: 13-17.
18. Strauss BH, Serruys PW, Bertrand ME, Puel J, Meier B, Goy JJ et al. Quantitative angiographic follow-up of the coronary wallstent in native vessels and bypass grafts (european expe-

rience – march 1986 to march 1990). Am J Cardiol 1992; 69: 475-481.
19. Ozaki Y, Violaris A, Hamburger J, Melkert R, Foley D, Keane D et al. Short- and long-term clinical and quantitative angiographic results with the new, less shortening wallstent for vessel reconstruction in chronic total occlusion: a quantitative angiographic study. J Am Coll Cardiol 1996; 28: 354-360.
20. von Birgelen C, Gil R, Ruygrok P, Pratio F, di Mario C, van der Giessen WJ et al. Optimized expansion of the Wallstent compared with the Palmaz-Schatz stent: on-line observations with two- and three-dimensional intracoronary ultrasound after angiographic guidance. Am Heart J 1996; 131: 1067-1075.
21. von Birgelen C, Airiian SG, de Feyter PJ, Foley DP, van der Giessen WJ, Serruys PW. Coronary wallstents show significant late, postprocedural expansion despite implantation with adjunct high-pressure balloon inflations. Am J Cardiol 1998; 82: 129-134.
22. de Jaegere P, Mudra H, Figulla H, Almagor Y, Doucet S, Penn I et al. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic resultas from the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC study). Eur Heart J 1998; 19: 1214-1223.
23. Vrints CJ, Bosmans J, Claeys MJ, Snoek JP. User-friendly and low-cost computer system for immediate review, analysis, and reconstruction of intracoronary ultrasound images. Cathet Cardiovasc Diagn 1998; 43: 357-362.
24. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med 1998; 339: 1665-1671.
25. Urban P, Macaya C, Rupprecht HJ, Kiemeneij F, Emanuelsson H, Fontanelli A et al. Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the multicenter aspirin and ticlopidine trial after intracoronary stenting (MATTIS). Circulation 1998; 98: 2126-2132.
26. De la Torre Hernández JM, Gomez González I, Rodríguez Entem F, Royuela N, Antolin Juarez FM, Zueco J et al. Evaluación con ultrasonografía intravascular de *stents* implantados sin predilatación (*stents* directos). Comparación de resultados según el tipo de lesión. Rev Esp Cardiol 2000; 53: 1335-1341.
27. Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vliedstra RE et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am Coll Cardiol 1992; 19: 267-274.
28. Hoffmann R, Mintz GS, Mehran R, Kent KM, Pichard AD, Satler LF et al. Tissue proliferation within and surrounding Palmaz-Schatz stents is dependent on the aggressiveness of stent implantation technique. Am J Cardiol 1999; 83: 1170-1174.
29. Edelman ER, Rogers C. Pathobiologic responses to stenting. Am J Cardiol 1998; 81: E4-E6.
30. Schwartz RS. Pathophysiology of restenosis: interaction of thrombosis, hyperplasia and/or remodeling. Am J Cardiol 1998; 81: E14-E17.
31. Roguin A, Grenadier E, Linn S, Markiewicz W, Beyar R. Continued expansion of the nitinol self-expanding coronary stent: angiographic analysis and 1-year clinical follow-up. Am Heart J 1999; 138: 326-333.
32. König A, Klauss V, Regar E, Rieber J, Casella G, Theisen K et al. Serial intravascular ultrasound and quantitative coronary angiography after self-expandable wallstent coronary artery implantation. Am J Cardiol 2000; 86: 1015-1018.
33. Kobayashi Y, Honda Y, Christie LG, Teirstein PS, Bailey SR, Brown CL et al. Long-term vessel response to a self-expanding coronary stent: a serial volumetric intravascular ultrasound analysis from the ASSURE trial. J Am Coll Cardiol 2001; 37: 1329-1334.