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Mechanisms of lumen enlargement after cutting balloon angioplasty for in-stent restenosis. An intravascular ultrasound study

Ultrasonograficzna ocena mechanizmów powiększania światła naczynia po angioplastyce balonem tnącym w leczeniu restenozy w stencie

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Abstract

Background: *The optimal treatment of in-stent restenosis (ISR) has not yet been identified. The aim of this study was to show the mechanisms of lumen enlargement with cutting balloon angioplasty in the treatment of ISR by intravascular ultrasound (IVUS).*

Material and methods: *A total of 40 consecutive patients of mean age 54 ± 10 years, in whom cutting balloon (CB) angioplasty was applied for ISR treatment, were included in the investigation. Ultrasonic images were recorded during an automatic pull-back manoeuvre at a constant speed of 0.5 mm/s. Serial IVUS studies were performed before and after intervention. The external elastic membrane, lumen, neointimal and stent areas were measured at intervals of 0.5 mm throughout the length of the stent and in the proximal and distal reference segments (5 mm from the stent edge).*

Results: *The use of CB led to a significant increase in lumen area and a decrease in the neointima area ($p < 0.05$). It was also of note that the mean increase in stent area was statistically significant. The external elastic membrane and plaque areas did not change significantly after the procedure (p = NS). Intravascular ultrasound assessment revealed that cutting balloon angioplasty led to a 29% reduction in the neointimal area. The stent area was enlarged by 24.9% and the external elastic membrane area increase was 14.2% after completion of the procedure (p = NS). Plaque areas at both reference segments showed a slight increase (p = NS).*

Conclusions: *Treatment of ISR with cutting balloon angioplasty is related to an increase in the lumen and stent areas, which is associated with neointima extrusion through the stent struts and axial redistribution of the neointima.* (Folia Cardiol. 2005; 12: 493–498)

in-stent restenosis, intravascular ultrasound, angioplasty

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Introduction

The widespread use of coronary stents has led to a specific new "disease", that of in-stent restenosis (ISR), which is reported with an incidence ranging from 8.3% to as much as 50% of cases [1, 2]. The main mechanism responsible for its development is neointimal formation [3]. So far, different techniques and approaches have been applied to limit the occurrence of ISR and several techniques have been evaluated to improve the artery lumen of restenotic stents [4]. The most popular techniques for ISR are plain balloon angioplasty, intracoronary brachytherapy [5] and cutting balloon angioplasty [6]. The aim of the study therefore was to show the mechanisms of lumen enlargement with cutting balloon angioplasty in the treatment of in-stent restenosis by intravascular ultrasound (IVUS).

Material and methods

Patient selection

For the purposes of the study, we retrospectively analyzed 40 consecutive patients of mean age 54 ± ± 10 years, in whom cutting balloon (CB) angioplasty was applied for ISR treatment.

Restenostic lesions in vessels with a reference diameter greater than 2.5 mm were considered for the study. Patients with either focal (< 10 mm in length) or diffuse (> 10 mm in length) in-stent restenosis were included, but patients with a totally occluded coronary segment were excluded from the study.

Initial stent procedures

The mean interval between initial stent implantation and the CB procedure for ISR treatment was 6 ± 3 months (range 3–12). The mean stent size was 3.21 ± 0.36 mm and its length was 15.7 ± ± 6.2 mm. The mean inflation pressure used for stent implantation was 15.4 ± 2.7 atm.

Procedures

Cutting balloon (Boston Scientific, Natick, MA, USA) is a non-compliant balloon varying from 10 to 15 mm in length with 3 or 4 microblades, depending on the size of the balloon. In the present study multiple inflations were performed at a pressure of up to 10–12 atm. In 16 cases out of 40 (40%) a 10 mm CB was used and in the remaining patients angioplasty was performed with a 15 mm balloon. The mean size of the CB was 3.55 ± 0.39 mm with a length of 13.12 ± 2.5 mm.

Intravascular ultrasound studies were performed both before and after intervention with a commercially available mechanical system (Boston Scientific Co, Natwitch, MS, USA) using 30 MHz or 40 MHz imaging catheters (Ultracross and Atlantis). The IVUS was performed in the same mode: after nitroglycerin administration, the imaging probe was positioned distally to the target lesion and pulled back at a constant speed of 0.5 mm/s with the use of a motorised pull-back device. IVUS images were recorded onto high-resolution s-VHS videotape for off-line analysis.

Quantitative angiographic and IVUS evaluation

Off-line quantitative coronary angiography (QCA) analyses were performed at the European Imaging Laboratory by 2 technicians, who were unaware of the IVUS measurements. Angiographic measurements were performed with a computer-assisted system using an automated edge detection algorithm (MEDIS Co, Eindhoven, Netherlands) with a dye-filled guiding catheter for calibration.

Intravascular ultrasound recordings were analysed for every second of videotape using commercially available software (Tape Measure, INDEC Co.). During the analysis each coronary segment was axially divided into several 0.5 mm segments.

Data from the analysis was presented as means and for the stented region included the minimal lumen area (LA), the total vessel area bordered by the external elastic membrane (EEM), the stent area (SA), the neointimal area (NA) defined as the echogenic material within the stent and the calculated SA minus the LA and plaque area (PA) measured as the plaque and media area between the EEM and the stent borders. The differences between procedural steps were calculated in the mean lumen areas, EEM, stent, neointimal and plaque areas. The analysis also encompassed two 5 mm reference segments in which lumen, EEM and PA were calculated.

The reproducibility of the IVUS and QCA measurements performed at the European Imaging Laboratory has already been reported [7, 8].

Statistical analysis

Continuous variables are expressed as mean ± ± standard deviation (SD) values. A two-tailed *t* test was used for the continuous variables. Linear regression analyses were performed to compare the study data. A value of $p < 0.05$ was considered statistically significant.

Table 1. Patient population (n = 40)

Tabela 1. Charakterystyka kliniczna pacjentów

Age (years)	54 ± 10
Male	89.2%
Diabetes	10.7%
Smoking	50.0%
Previous myocardial infarction	45.7%
Vessel treated	
left anterior descending artery	28 (70%)
left circumflex artery	3 (7.5%)
right coronary artery	9 (22.5%)

Table 2. Angiographic and procedural characteristics

Tabela 2. Dane angiograficzne i proceduralne

QCA measurements pre treatment	
MLD [mm]	0.9 ± 0.25
Ref. D. [mm]	2.88 ± 0.36
%DS (%)	68.7 ± 14.5
Lesion length [mm]	12.3 ± 4.1
QCA measurements post treatment	
MLD [mm]	2.48 ± 0.55
Ref. D. [mm]	3.01 ± 0.44
%DS (%)	17.6 ± 10.1
Acute gain [mm]	1.58 ± 0.67
BA/artery ratio	1.22 ± 0.24
Inflation pressure [atm]	8.5 ± 2.1

Table 3. Intravascular ultrasound results from the treated segment (n = 40)

Tabela 3. Wyniki ultrasonografii wewnątrzwieńcowej w badanych segmentach naczyń

Distal reference segment	
EEM area pre [mm^2]	10.42 ± 4.36
EEM area post [mm^2]	10.93 ± 4.36
LA area pre [mm^2]	5.04 ± 1.96
LA area post [mm^2]	4.57 ± 1.97
PA area pre [mm^2]	5.38 ± 3.06
PA area post [mm^2]	6.36 ± 3.00
Restenotic lesion	
EEM area pre [mm^2]	16.42 ± 5.57
EEM area post [mm^2]	18.76 ± 5.84
LA area pre [mm^2]	4.11 ± 1.37
LA area post [mm^2]	6.31 ± 2.02*
SA area pre [mm^2]	7.93 ± 2.40
SA area post [mm^2]	9.91 ± 3.01*
PA area pre [mm^2]	8.42 ± 3.43
PA area post [mm^2]	8.83 ± 3.32
NA area pre [mm^2]	4.27 ± 1.96
NA area post [mm^2]	3.31 ± 1.42*
Proximal reference segment	
EEM area pre [mm^2]	16.28 ± 6.45
EEM area post [mm^2]	16.82 ± 6.64
LA area pre [mm^2]	7.35 ± 2.95
LA area post [mm^2]	7.15 ± 2.75
PA area pre [mm^2]	8.92 ± 4.75
PA area post [mm^2]	9.66 ± 4.88

*$p < 0.05$ pre vs. post; EEM — external elastic membrane; LA — lumen area; PA — plaque area; SA — stent area

Results

The demographic, clinical and angiographic characteristics and the procedural data are presented in Tables 1 and 2. Pre-interventional IVUS assessment showed a diffuse pattern of ISR in 64% of cases.

Table 3 refers to the IVUS results obtained before and after intervention. The use of CB led to a significant increase in lumen area and a decrease in neointima area ($p < 0.05$). It is also of note that the mean increase in stent area was statistically significant. The EEM and plaque areas did not change significantly after the procedure (p = NS)

Intravascular ultrasound assessment revealed that cutting balloon angioplasty led to a 29% reduction in the neointimal area. The stent area enlarged by 24.9% and the EEM area increase was 14.2% after procedure completion (p = NS). It was notable that lumen improvement (increase) was only 53% (Fig. 1).

Figure 2 refers to the mean neointima area decrease in two subsets of patients, those with and those without a mean IVUS stent area of 9.0 mm^2 (using the MUSIC trial criteria). The neointima decrease was larger in patients with a mean stent area of over 9.0 mm^2 but the difference was not significant.

Reference segment analysis

Introvascular ultrasound analysis obtained in the reference segments revealed that there was a trend to lumen area decrease and plaque area increase. The percentage of PA increase was 18.2% in the distal reference segment and 8.2% in the proximal reference segment.

Discussion

The major findings of the present study are that the main mechanism of lumen enlargement with CB angioplasty consists of an increase in the lumen and stent areas which is related to neointima extrusion through the stent struts and its axial redistribution.

Uncontrolled arterial smooth muscle proliferation is mainly responsible for the development of ISR [3, 9]. Several systemic, angiographic and IVUS

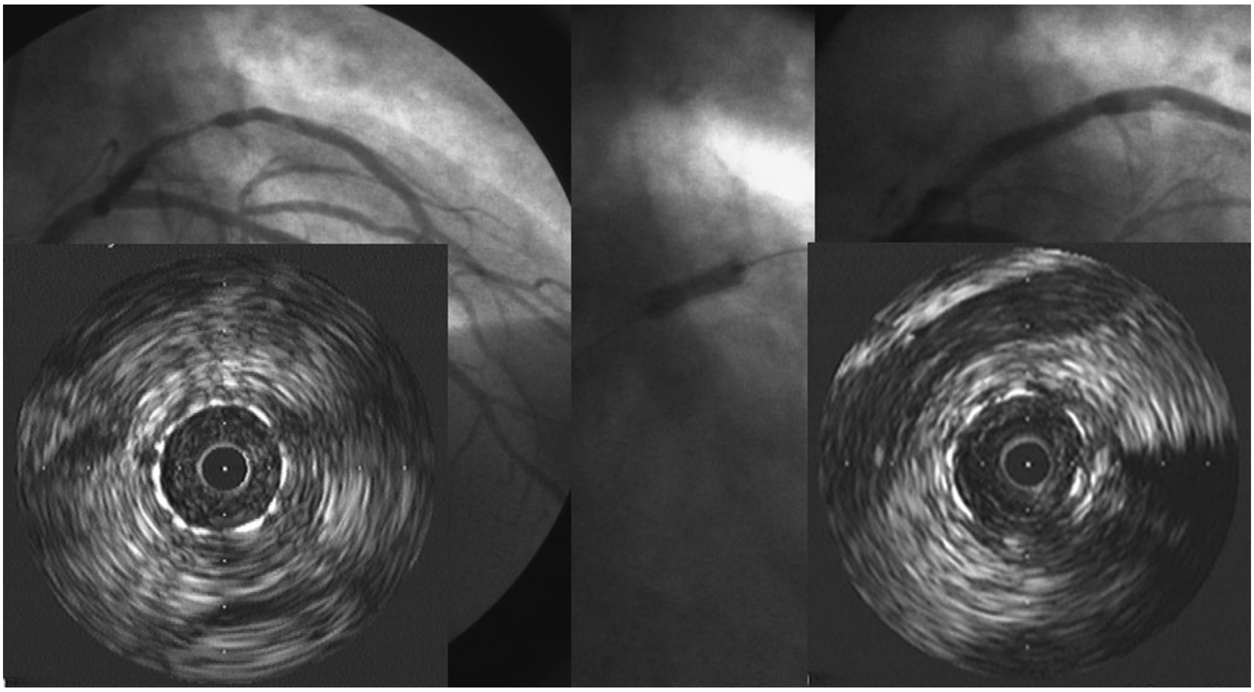

Figure 1. Example of the procedure performed in studied group

Rycina 1. Przykład zabiegu wykonanego w badanej populacji

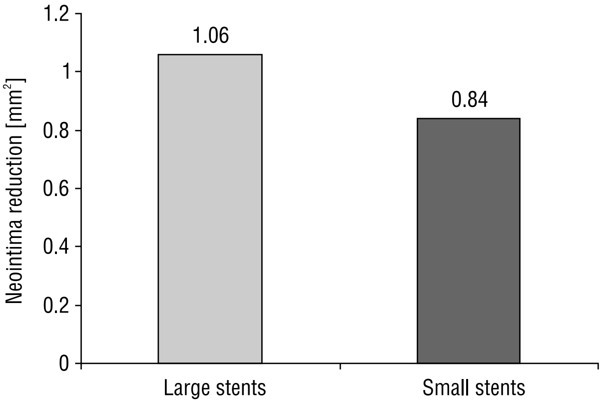

Figure 2. A comparison of the neointima area change obtained in patients with a mean stent area > 9.0 mm^2 (large stents) with patients with a mean stent area < 9.0 mm^2 (small stents)

Rycina 2. Porównanie zmiany pola neointimy u pacjentów ze średnim polem światła stentu powyżej 9,00 mm^2 („duże stenty") z chorymi ze średnim polem światła stentu poniżej 9,00 mm^2 („małe stenty")

factors have been proposed as predictors of ISR [10]. So far, no optimal treatment of ISR has been developed, although some approaches are used in clinical practice such as POBA, debulking techniques (rotablation or DCA) and cutting balloon angioplasty, excimer laser angioplasty or stenting, recently with drug eluting stents [10]. Of course, the most popular method for ISR treatment is simple balloon inflation, alternatively with CB, which provides a better angiographic and clinical outcome than POBA [4].

Previous studies concerning the mechanisms of lumen enlargement after ISR treatment have led to a different observation, especially in the case of CB. Ahmed et al. [11] showed that the main mechanisms of lumen enlargement with CB are related to neointima extrusion through the stent struts and its axial redistribution into reference segments, as reported in our study. On the other hand, Muramatsu et al. [12] concluded that CB inflation led to a decrease in plaque area with a constant stent and EEM area. In this study both EEM and stent area increase and, furthermore, axial neointima redistribution were demonstrated as playing a significant role in lumen enlargement. The stent area increased by 24.9%, more than in the previous study by Kinoshita et al. [13], who obtained only a 10.6% stent increase. However, it should be remembered that CB is a non-compliant balloon, designed for this kind of work. Prompter selection of CB size and its relation to the artery may play a crucial role in the acute results of CB angioplasty. The use of a BA/artery ratio greater then 1.0 may help to achieve more gain in lumen.

On the basis of the results of present and previous studies [11, 15], the possibility cannot be excluded that, besides a plaque increase resulting from neointima extrusion, some kind of native plaque compression or axial redistribution is present. This is supported by the finding that the increase in the EEM area is not equal to the stent plus plaque area increase in the stented segment after the procedure. Recently it has been proved that plaque compression is partially responsible for lumen enlargement after stenting [16]. It is, therefore, reasonable to include this mechanism as one of the features of lumen enlargement after ISR treatment.

Conclusions

Treatment of ISR with cutting balloon angioplasty is related to an increase in lumen and stent areas which is related to neointima extrusion through the stent struts and axial redistribution of the neointima.

Streszczenie

Wstęp: *Obecnie nie ma optymalnego sposobu leczenia restenozy w stencie. Celem poniższej pracy jest ultrasonograficzna ocena mechanizmów powiększenia światła naczynia po zabiegu angioplastyki balonem tnącym (CB) u chorych z restenozą w stencie.*

Materiał i metody: *Do badania włączono 40 (średni wiek 54 ± 10 lat) kolejnych chorych z restenozą w stencie, u których do leczenia użyto balonu tnącego. Badanie metodą ultrasonografii wewnątrzwieńcowej (IVUS) wykonywano zarówno przed interwencją, jak i po niej, używając automatycznego przesuwu sondy przy stałej prędkości 0,5 mm/s. Do analizy włączono pole całkowite naczynia, pole światła naczynia, pole blaszki miażdżycowej, pole neointimy i pole światła stentu, które zostały zmierzone co 0,5 mm na całej długości stentu oraz w obrębie 5 mm segmentów referencyjnych naczynia.*

Wyniki: *Stwierdzono, że użycie CB prowadzi do istotnego przyrostu pola światła naczynia i istotnej redukcji neointimy ($p < 0,05$). Ponadto, zaobserwowano istotny przyrost pola stentu ($p < 0,05$). Całkowite pole naczynia oraz pole blaszki miażdżycowej nie zmieniły się istotnie po zabiegu ($p = NS$). Zastosowanie IVUS pokazało, że angioplastyka CB prowadzi do 29-procentowej redukcji neointimy, 24,9-procentowego zwiększenia pola stentu oraz 14,2-procentowego przyrostu całkowitego pola naczynia. Analiza zmian w segmentach referencyjnych ujawniła trend w kierunku przyrostu blaszki, który nie był istotny statystycznie.*

Wnioski: *Angioplastyka balonem tnącym prowadzi do istotnego przyrostu pola światła naczynia oraz zwiększenia pola stentu, co wiąże się z przemieszczeniem neointimy pomiędzy elementy stentu i w kierunku segmentów referencyjnych.* (Folia Cardiol. 2005; 12: 493–498)

restenoza w stencie, ultrasonografia wewnątrzwieńcowa, angioplastyka

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