Serial optical coherence tomographic observation of neointimal tissue after bare-metal and everolimus-eluting stent in porcine coronary artery

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Serial optical coherence tomographic observation of neointimal tissue after bare-metal and everolimus-eluting stent in porcine coronary artery

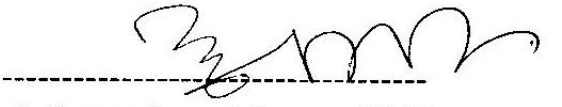
Directed by Professor Myeong-Ki Hong

The Doctoral Dissertation
submitted to the Department of Medicine
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Doctor of Philosophy

Hoyoun Won

June 2014

This certifies that the Doctoral Dissertation of Hoyoun Won is approved.



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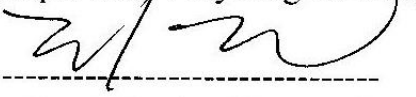

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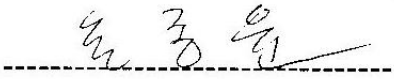

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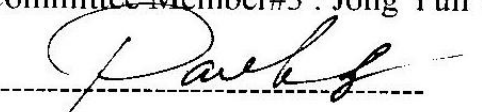

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June 2014

ACKNOWLEDGEMENTS

First of all, I would like to give my sincere thanks to my honorific supervisor, Professor Myeong-Ki Hong, who accepted me as his Ph.D. student without any hesitation. Thereafter, he offered me so much advice, patiently supervising me, and always guiding me in the right direction. I have learned a lot from him, without his help I could not have finished my dissertation successfully.

Special thanks are also given to prof. Jung-Sun Kim. He has supported me not only by providing a research, but also academically and emotionally through the rough road to finish this thesis.

I really appreciated prof. Namsik Chung, prof. Yangsoo Jang, prof. Donghoon Choi, prof. Moon-Hyoung Lee, prof. Jong-Won Ha, prof. Young-Guk Ko, prof. Hui-Nam Pak, prof. Boyoung Joung, prof. Hyuk-Jae Chang, prof. Sang-hak Lee, prof. Sungha Park, prof. Byeong-Keuk Kim, prof. Chi Young Shim, prof. Dong-Ho Shin, prof. Jae-Sun Uhm for their advice and encouragement, guiding me into the territory of cardiology. Also, I would like to thank to my thesis committee, Professors Sung Yun Lee, Jong Yun Won and

Jong-Chul Park for their helpful advice and suggestions in general.

I would like to thank all my colleagues during fellowship course who offered assistance, discussion and the beautiful memory of friendship in division of cardiology at Severance Cardiovascular Hospital.

I love and give special thanks to my parents for their invaluable support and love. I owe a great debt of love to my parents. I also owe a deep appreciation to my mother in law for her encouragement. Most importantly, I wish to thank my loving wife, Minjung Choi and my little angel, Jiwoo for their endless amusement, love and dedication during my years of graduate study. I cannot imagine trying to accomplish such a task without their love and support.

2014.6.

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ABSTRACT

Serial optical coherence tomographic observation of neointimal tissue after bare-metal and everolimus-eluting stent in porcine coronary artery

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Objectives: To evaluate serial changes in neointimal tissues between everolimus-eluting stent (EES) and bare-metal stent (BMS) in normal porcine coronary artery using optical coherence tomography (OCT).

Background: Serial changes in neointimal tissue after drug-eluting stent implantation have not been sufficiently investigated using OCT.

Methods: Serial (1, 3 and 6 months follow-up after stent implantation) OCT examinations were performed in 15 swine with 15 BMS- and 15 EES-treated lesions in normal porcine coronary arteries. Qualitative and quantitative changes of neointimal tissues in stented segments with maximal percentage of cross-sectional area stenosis of neointima at 1 month follow-up were serially evaluated.

Results: In BMS-implanted lesions, neointimal volume did not significantly change from median 6.5 (interquartile (IQR) 4.7-7.6) mm^3 to 6.9 (IQR 4.6-8.2) mm^3, 6.4 (IQR 4.3-7.4) mm^3 at 1, 3 and 6 months follow-up (p=0.882). At different time point of 1, 3 ant 6 months, neointimal tissue appearance was mainly the homogeneous pattern

(80.0%, 93.3% and 100%, respectively), while the layered pattern decreased (20.0%, 6.7% and 0%, respectively). On the other hands, in EES-implanted lesions, neointimal volume increased median 4.8 (IQR 4.1-7.6) mm^3 to 9.8 (IQR 5.7-15.1) mm^3 between 1 and 3 months ($p<0.001$), but significantly decreased to 8.6 (IQR 6.0-11.2) mm^3 between 3 and 6 months ($p=0.007$). Between 1 and 3 months, the layered pattern of neointima increased from 26.7% to 66.7%, but deceased to 20.0% between 3 and 6 months.

Conclusion: In this animal model, this OCT study showed that EES had a biphasic pattern of neointimal amounts which was correlated with change of neointimal morphology.

Key words : neointima, optical coherence tomography, drug-eluting stent

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I. INTRODUCTION

The development of drug-eluting stent (DES) has significantly reduced the incidence of in-stent restenosis compared with bare-metal stent (BMS).[1,2] However, even in the DES era, in-stent restenosis remains a significant clinical problem, particularly in high-risk patients.[3] Optical coherence tomography (OCT) is a high-resolution imaging tool to be ideal for evaluation of neointimal tissue characteristics as well as strut coverage of coronary stent.[4-6] The everolimus-eluting stent (EES) is a second-generation DES with the target lesion revascularization rate as low as 4.7% during 5-year clinical follow up.[7] However, there was little data for temporal change of neointimal tissue after EES implantation. The purpose of this study was to evaluate serial changes of OCT-based neointimal tissue in stented segments between 1, 3 and 6 months after EES implantation compared to BMS implantation in normal porcine coronary arteries.

II. MATERIALS AND METHODS

1. Study design

All animals received humane care in compliance with the Animal Welfare Act and the "Guide for the care and use of laboratory animals" formulated by the Institute of Laboratory Animal Research.[8] The study protocol was approved by the local institutional animal care and use committee. A total of 15 swine (25 to 30 kg) were studied for 6 months to evaluate neointimal tissue following EES implantation serially. Two types of stent were implanted: EES (Xience Prime, 3.0 x 12mm, Abbott Vascular, Santa Clara, CA, USA) as a target stent and BMS (Blazer, 3.0 x 13mm, OrbusNeich, Hongkong, China) as a control stent. Each stent was deployed in left anterior descending artery or right coronary artery. At the time of stent deployment, each stent was systematically randomized to each coronary artery in each animal. Follow-up angiography with OCT was serially performed at 1, 3 and 6 months after stent implantation.

2. Procedural description

All animals were pre-medicated with 100 mg of aspirin and 300 mg of clopidogrel at least 12 hours before the procedure. Anesthesia was achieved with intramuscular injection of ketamine (20mg/kg) and xylazine (2mg/kg). Under the condition of an adequate anesthetic status, the animals were intubated and inhaled isoflurane (1-2%) which was delivered through a precision vaporizer and a circle absorption breathing system with periodic arterial blood gas monitoring. Under sterile conditions, an arteriotomy of the carotid artery was performed and a 6-Fr vascular

access sheath was introduced into the carotid artery. Vital signs with surface electrocardiography were continuously monitored and were recorded at approximately 20-min intervals. Unfractionated heparin of 5,000 to 10,000 IU was administered to maintain an activated clotting time of 250 to 300 seconds. Under fluoroscopic guidance, stent implantation was performed with a stent-to-artery ratio of 110% to 120% overstretch for full apposition at the predetermined sites using conventional techniques. After stent implantation, repair of carotid arteries for hemostasis and closure of the incision site for next use of carotid arteries were performed with adequate suture material. All animals received 100 mg of aspirin and 75 mg of clopidogrel daily after stent implantation. They were fed a regular diet throughout the study.

3. OCT procedure and analysis

OCT was performed with the C7-XR™ imaging systems (LightLab Imaging, Inc., St. Jude Medical, St. Paul, MN, USA). The OCT catheter was pulled back at 20 mm/s and OCT images were generated at 100 frames/s, while contrast medium was continuously flushed through a guiding catheter at a rate of 4 to 5 ml/s for 3 to 4 seconds. Images were continuously acquired and stored digitally for subsequent analysis. All OCT images were analyzed at a core laboratory (Cardiovascular Research Center, Seoul, Korea) by analysts who were blinded to procedural information. Cross-sectional OCT images were analyzed at 1-mm intervals. Stent and luminal cross-sectional areas (CSA) were measured and neointimal hyperplasia (NIH) CSA was calculated by subtracting the luminal CSA from the stent CSA. Percentage of NIH CSA was calculated as NIH

CSA divided by stent CSA. NIH thickness was measured as the distance between the strut with a line perpendicular to the neointima and the endoluminal surface of neointima. NIH volume was calculated as NIH CSA × length. The maximal NIH site with 2 mm proximal and distal adjacent portion in stented segment was serially compared to their corresponding segment on the basis of maximal NIH site at 1 month follow up. The serial comparison was done by matching the length from the stent edge and anatomical features such as side branch.

Neointimal tissue characteristics were qualitatively classified into homogeneous, heterogeneous and layered pattern if mean neointimal thickness was ≥ 20 μm.[9] Homogeneous pattern was defined as uniform optical properties of neointima tissue without focal variation in backscattering pattern. Heterogeneous pattern was defined as focal change of optical properties and various backscattering patterns. Layered pattern refers to concentric layers with different optical properties, namely an adluminal high scattering layer and abluminal low scattering layer (Figure 1).

4. Quantitative angiographic analysis

Quantitative coronary angiography analysis was performed using an offline computerized quantitative coronary angiographic system (CASS system, Pie Medical Imaging, Maastricht, Netherlands) in an independent core laboratory (Cardiovascular Research Center, Seoul, Korea). The minimal lumen diameter and reference diameter of treated coronary lesions were measured in the view with the narrowest lumen and the least amount of foreshortening.

5. Statistical analysis

Continuous variables were expressed as a mean ± standard deviation (SD). Wilcoxon rank test and Friedman test was used to compare variables with longitudinal manner. The categorical variables were expressed as both number and percentage, and were compared using Fisher's exact-test. Data were analyzed with the SPSS 18.0 software for Windows (SPSS, Chicago, IL., USA). A p-value < 0.05 was considered statistically significant

III. RESULTS

EES was implanted in 8 left anterior descending arteries and 7 right coronary arteries; BMS was deployed in 7 left anterior descending arteries and 8 right coronary arteries. Serial OCT evaluation of NIH was finally assessed in a total of 15 BMS and 15 EES implanted in coronary arteries of 15 porcine at 1, 3 and 6 months follow-up. Serial angiographic and OCT findings are shown in Table 1. In the analysis of whole stented segment, while mean NIH thickness did not significantly change along time course at 1 month (median 167.9 (IQR 127.0-203.9) μm), and decreased along time course at 3 and 6 months (163.6 (IQR 131.9-229.4) μm and 169.8 (IQR 122.7-211.1) μm, p=0.267) in BMS, it was maximal at 3 months (276.5 (IQR 172.2-428.1) μm), then significantly decreased at 6 months (269.6 (IQR 199.9-396.4) μm, p<0.001) in EES. In the analysis of maximal NIH segment at 1 month, serial changes of NIH volume of BMS and EES are shown in Figure 2. In BMS-implanted lesions, NIH volume decreased continuously from 6.7±2.4mm^3 to 6.5±2.2mm^3, 6.2±2.1mm^3 at 1, 3 and 6 months

follow-up (p=0.504). At different time point of 1, 3 ant 6 months, neointimal tissue appearance was mainly the homogeneous pattern (80.0%, 93.3% and 100%, respectively), while the layered pattern decreased (20.0%, 6.7% and 0%, respectively) (Figure 3). On the other hands, in EES-implanted lesions, NIH volume increased 5.8±2.5mm^3 to 10.3±5.0mm^3 between 1 and 3 months, but significantly decreased to 8.6±3.5mm^3 between 3 and 6 months (p=0.004) (Figure 2). Between 1 and 3 months, the layered pattern of neointima increased from 26.7% to 66.7%, but deceased to 20.0% between 3 and 6 months (Figure 3). Figure 4 and 5 shows typical OCT images of serial NIH changes in BMS- and EES-implanted coronary arteries, respectively.

Table 1. Quantitative coronary angiographic and optical coherence tomographic findings of the entire stent segment at 1, 3 and 6 months after stent implantation

	Bare-metal stent (n=15)			Everolimus-eluting stent (n=15)		
	1 month	**3 months**	**6 months**	**1 month**	**3 months**	**6 months**
Quantitative coronary angiography analysis						
Proximal reference, mm	2.7 (2.6-3.1)	2.8 (2.6-3.2)	2.8 (2.5-3.2)	2.9 (2.7-3.2)	3.0 (2.6-3.1)	2.7 (2.4-3.1)
Distal reference, mm	2.6 (2.4-2.8)	2.6 (2.3-3.0)	2.5 (2.2-2.9)	2.6 (2.4-2.8)	2.5 (2.4-2.7)	2.5 (2.3-2.7)
Minimal lumen diameter, mm	2.2 (2.0-2.5)	2.2 (2.1-2.4)	2.2 (2.0-2.4)	2.4 (2.0-2.6)*	1.7 (1.4-2.3)	1.8 (1.5-2.2)
Optical coherence tomography findings						
Neointimal thickness, μm	167.9 (127.0-203.9)	163.6 (131.9-229.4)	169.8 (122.7-211.1)	120.6* (93.8-203.9)	276.5 (172.2-428.1)	269.6 (199.9-396.4)
Stent area, mm^2	5.9 (5.3-6.8)	5.9 (5.4-7.0)	5.8 (5.2-6.8)	6.5 (5.1-6.9)	6.5 (5.4-7.0)	6.3 (5.0-6.9)
Lumen area, mm^2	4.2 (3.8-5.6)	4.7 (4.0-5.4)	4.4 (3.8-5.3)	4.9 (4.1-5.8)*	3.8 (3.0-4.9)	3.8 (3.2-4.5)
Neointimal area, mm^2	1.3 (1.1-1.8)	1.4 (1.0-1.9)	1.4 (0.9-1.7)	1.0 (0.9-1.8)*	2.3 (1.4-3.6)	2.4 (1.6-3.1)
Percentage of neointimal hyperplasia area, %	24.0 (19.2-28.6)	22.9 (17.3-30.9)	23.2 (16.6-30.0)	16.7 (12.9-28.1)*	37.0 (24.2-53.7)	35.4 (31.8-45.0)

* $p<0.05$, by using Friedman test

Table 2. Optical coherence tomographic findings of the maximum neointima site at 1, 3 and 6 months after stent implantation

	Bare-metal stent (n=15)			Everolimus-eluting stent (n=15)		
	1 month	**3 months**	**6 months**	**1 month**	**3 months**	**6 months**
Quantitative analysis						
Stent volume, mm^3	24.3 (21.4-27.4)	24.3 (21.8-26.9)	22.7 (21.4-26.5)	25.5 (20.7-27.2)	25.5 (20.4-27.6)	24.7 (19.9-27.9)
Lumen volume, mm^3	16.7 (14.7-20.2)	17.5 (15.7-20.6)	17.6 (14.4-20.8)	18.7 (16.5-21.4)*	12.6 (11.5-17.6)	15.5 (13.3-18.3)
Neointima volume, mm^3	6.5 (4.7-7.6)	6.9 (4.6-8.2)	6.4 (4.3-7.4)	4.8 (4.1-7.6)*	9.8 (5.7-15.1)	8.6 (6.0-11.2)
Qualitative analysis						
Homogeneous, %	12 (80.0)	14 (93.3)*	15 (100)	11 (73.3)	5 (33.3)	12 (80.0)
Layered, %	3 (20.0)	1 (6.7)*	0 (0)	4 (26.7)	10 (66.7)	3 (20.0)

* $p<0.05$, by using Friedman test in continuous variables or Fisher's exact-test in categorical variables between bare-metal stent and everolimus-eluting stent

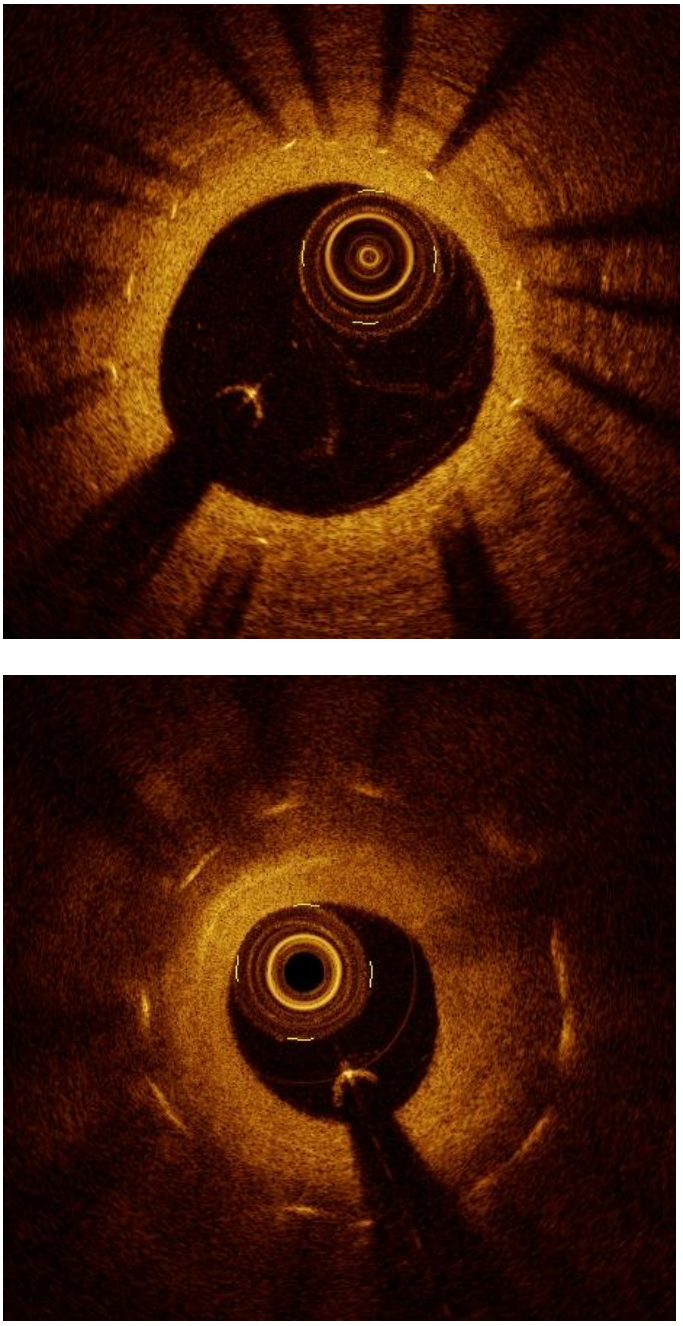


Figure 1. Representative optical coherence tomographic images of neointima, homogeneous pattern (top) and layered pattern (bottom).

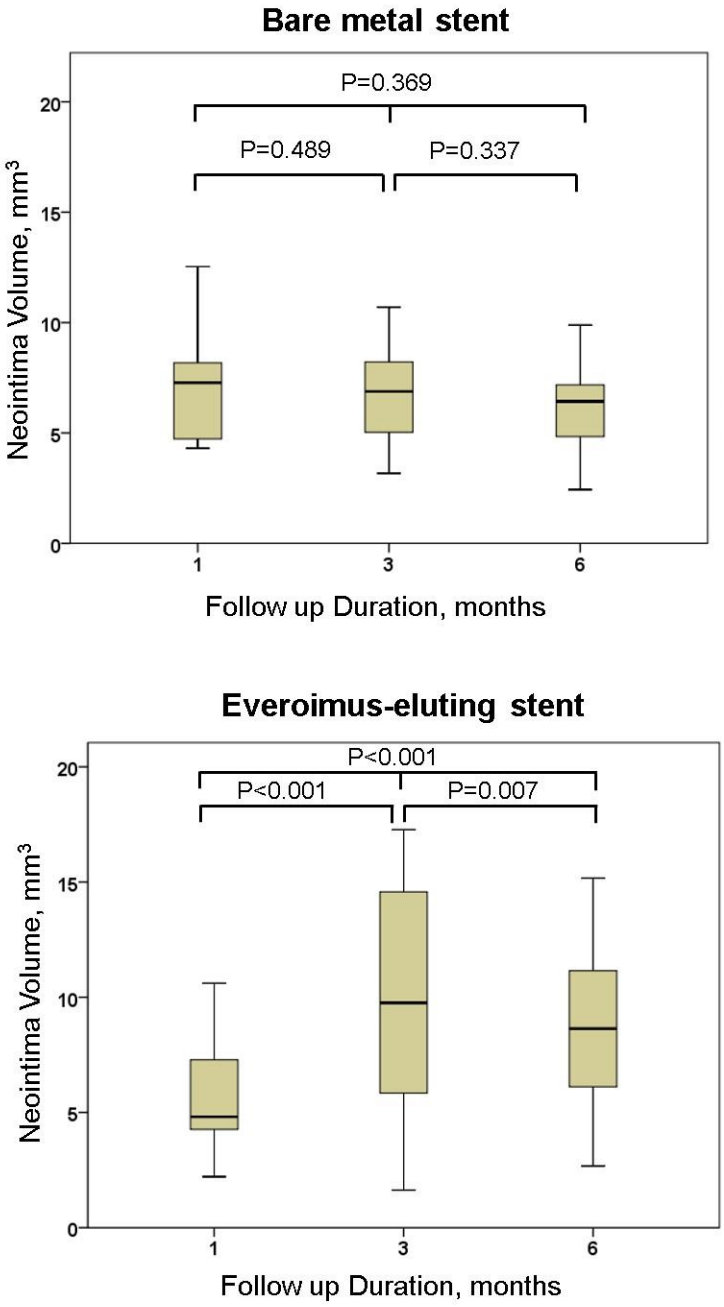


Figure 2. Serial change of neointimal volume at the segment with maximal amounts of neointimal hyperplasia at 1 month follow-up.

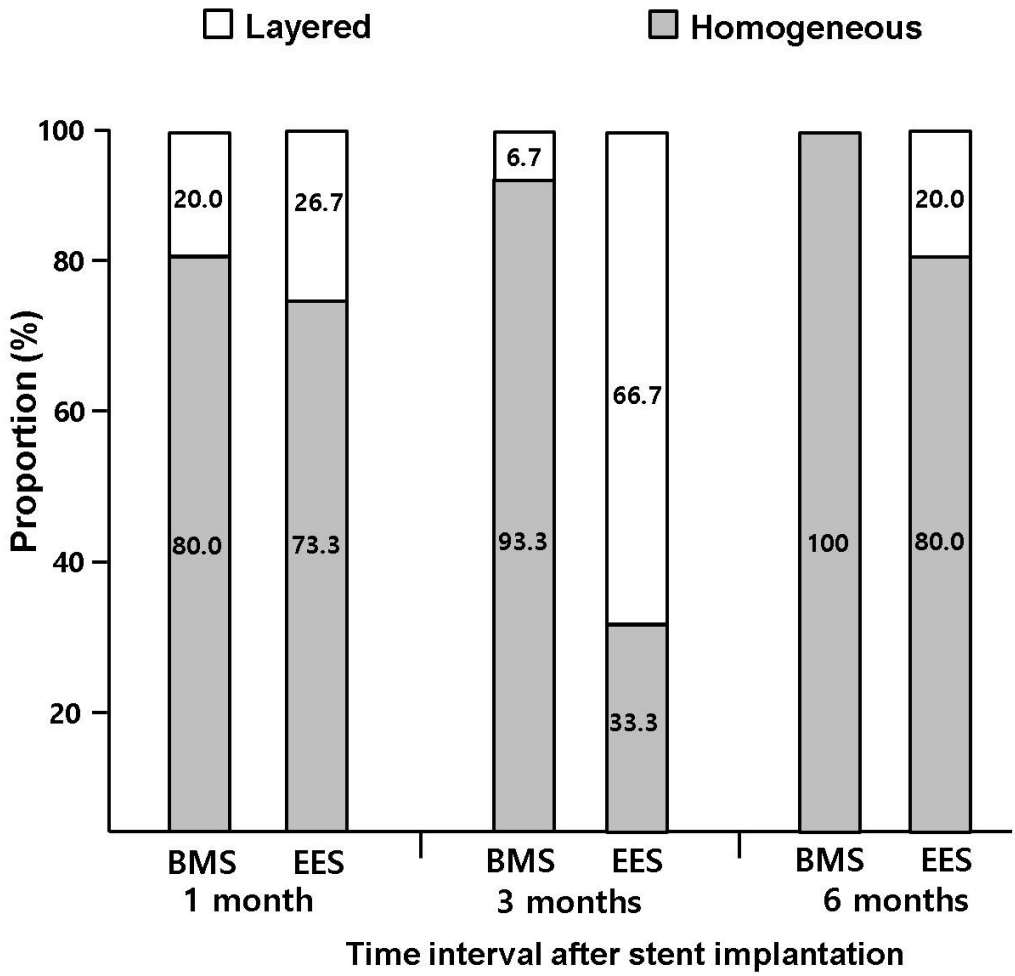
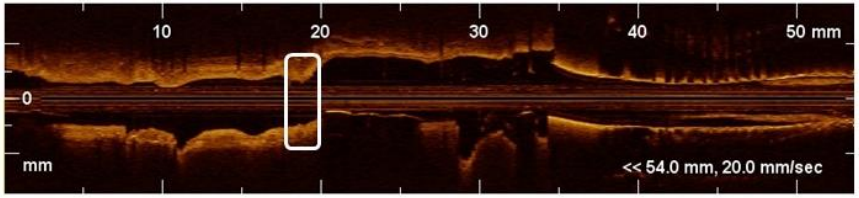


Figure 3. Serial change of neointimal patterns at the segment with maximal amounts of neointimal hyperplasia at 1 month follow-up. BMS, bare-metal stent; EES, everolimus-eluting stent

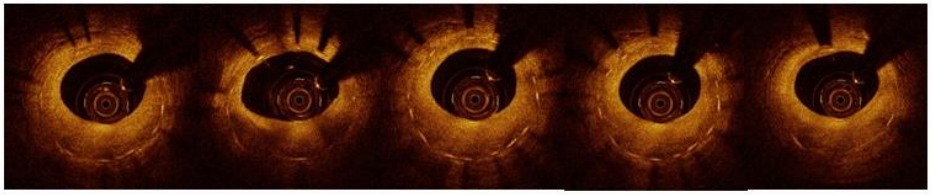
Bare Metal Stent



1 Month

Layered

NIH vol. 10.0mm^3



3 Months

Homogeneous

NIH vol. 8.8mm^3

6 Months

Homogeneous

NIH vol. 6.4mm^3

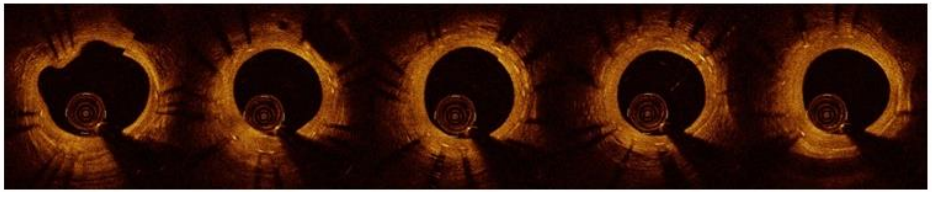


Figure 4. Examples of neointimal volume and patterns at the segment with maximal amounts of neointimal hyperplasia at 1, 3 and 6 months following bare-metal stent implantation. NIH, neointimal hyperplasia

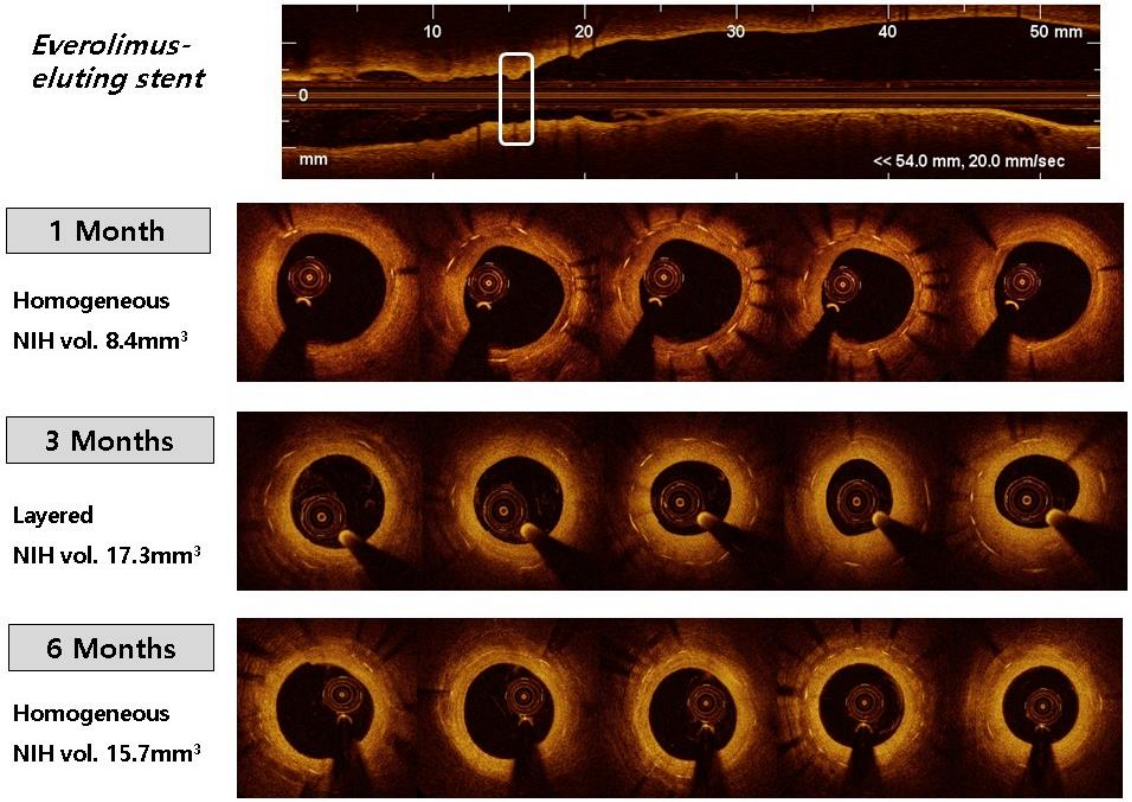


Figure 5. Examples of neointimal volume and patterns at the segment with maximal amounts of neointimal hyperplasia at 1, 3 and 6 months following everolimus-eluting stent implantation. NIH, neointimal hyperplasia

IV. DISCUSSION

Using serial (1, 3 and 6 months follow-up) OCT in the non-atherosclerotic porcine coronary artery model, the present study showed that (1) a biphasic neointimal response of EES consisted of an early progression phase and late regression phase and (2) this quantitative changes of neointima were correlated with morphological changes of neointima from layered pattern to homogeneous pattern.

Serial quantitative neointimal change of BMS has been well evaluated in human studies. In BMS, long term angiographic luminal response was a triphasic pattern which consisted of restenosis phase at early period until 6 months, regression phase at intermediate period between 6 months and 3 years and late re-narrowing phase after 4 years.[10] The results of intravascular ultrasound studies were also consistent with those of angiographic study.[11,12] One intravascular ultrasound study reported that that mean neointimal CSA significantly decreased from 2.6±1.0 to 2.3±0.9 mm^2 between 6 and 24 months after BMS-treated patients.[11] The result of BMS-implanted lesions in the present study is in a line with the results from the previous studies.[10-12]

However, information for long term serial change of neointima was sparse in DES. Sousa et al. firstly reported that there was a triphasic restenotic pattern of the slow release sirolimus-eluting stent (SES) in a long term IVUS study, an early restenotic phase before 1 year, an intermediate regression phase between 1 and 2 years and a late re-restenotic phase after 2 years.[13] In a study performed earlier than Sousa's study, angiographic late loss in stent was decreased from 0.25±0.28 mm at 6 month follow-up to 0.20±0.24 mm at 20 month follow-up, but the difference was not statistically

significant.[13] Park et al. recently reported there was a biphasic neointimal response after SES, PES and zotalorimus-eluting stent implantation in a serial angiographic study for 2 years.[14] Among 165 DES treated lesions, in-stent luminal diameter was decreased in 45 lesions, but increase in 2 lesions until 9 months after DES implantation. However, between 9 and 24 months, the luminal diameter was decreased in 27 lesions and increased in 4 lesions with significant increase in mean luminal diameter. This change similarly occurred in all three type of stent. Conversely, in TAXUS II trial, angiographic late loss was not significantly changed between 6 and 24 months, but in-stent neointimal volume by IVUS was increased in paclitaxel-eluting stent (PES) during the same period.[15] However, in the EES, SPIRIT II trial reported mean angiographic late loss and in-stent neointimal volume was progressed between 6 and 24 months after index procedure.[16] As our acknowledgements, this is the first report to show a biphasic neointimal response of EES. The neointimal volume was peak at 3 month after EES implantation in swine coronary and then decreased by 6 month follow up.

Neointimal regression occurred with morphological shift from layered pattern to homogeneous pattern. The mechanism of the regression in neointimal hyperplasia was not clearly understood. In OCT image, neointima with rich smooth muscle cells and dense collagen fibers has a high backscatter signal, so that is shown as high optical intensity. Besides, extracellular matrix or myxomatous tissue such as proteoglycan or fibrin rich neointima with little smooth muscle cells has a low backscatter signal, so that is shown as lucent signal.[17] The homogeneous pattern with a high optical intensity was usually observed in ISR of BMS.[18] Layered pattern was consisted of high intense

inner layer with smooth muscle cells and low intense outer layer with extracelluar material rich lesion.[17] The present study supports that neointimal stabilization from immature tissue such as fibrin near strut, rich extra-cellular matrix and inflammatory cells to maturation with rich smooth muscle cells may a role for the neointimal regression.[19] Layered and heterogeneous pattern is shown more frequent in ISR of DES than that of BMS.[18] However, we did observe no heterogeneous pattern which shows various intensities.

1. Accuracy of OCT as an imaging tool for evaluation of neointimal hyperplasia

The OCT has been recognized as promising intravascular imaging modality due to high resolution. The OCT for the quantitative assessment has been well validated. Compared to histology, OCT showed a high accuracy for the evaluation of neointimal thickness after stent implantation with 0.726 of correlation efficiency and mean 7 μm of variation.[20] In a preclinical study with swine model, the difference of neointimal area and thickness by OCT was respectively 6.4% and 3.3% higher than those by histology ($p<0.001$ and $p=0.11$).[5] The correlation coefficiency between OCT and histology for the evaluation of neointimal area and thickness was 0.804 and 0.789, respectively.[5] The larger neointima of OCT was considered due to tissue shrinkage of histology. A recent study with an atherosclerotic rabbit model showed more excellent correlation between OCT and histology for the quantitative measurement of neointima than earlier two studies ($R^2 = 0.93$ for neointimal area and $R^2 = 0.93$ for neointimal thickness).[21] A small

degree of neointimal hyperplasia which was less than thirty percentage of the stent area was also able to be accurately measured by OCT (r=0.922 compared to histology).[22]

2. Limitation

This study was based on non-atherosclerotic porcine coronary artery model. Compared to diseased arterial model, the disadvantages of the present model may not reflect patient characteristics, such as the diabetes mellitus, the influence of medication and atherosclerosis, which can affect stent healing process. Furthermore, major factor of human atherosclerosis such as calcification and necrotic core was not replicated in this study. Therefore, the results of the present study may need to be the caution for interpretation. However, the normal swine coronary model is a widely used research modality for the investigation of in-stent restenosis.[5,22,23] Another limitation is the possibility of the variation among the follow up OCT image. Although we used the same OCT machine with same protocol of contrast injection at each follow up, there was a little variability of stent length on the OCT image. However, we tried to follow as exact maximal neointimal segment at 1 month as possible based on the reference point with both edge of the stent and branches on the cross-sectional images. In addition, there was a variety of degrees of neointimal proliferation among different swine or even different coronaries in the same animal. Finally, we did not compare the OCT images with the histology at every follow up. However, as our aim of this study was to evaluate the serial change of neointimal hyperplasia in the same stent, it was not possible to

sacrifice the animal for the histology. Also, the correlation between the OCT image and histology was already mentioned in the discussion.

V. CONCLUSION

In conclusion, the current study suggested that the neointimal hyperplasia in EES was regressed during late phase, although the neointima of BMS was regressed from early phase. The regression of neointima was occurred with the morphological change of neointimal from layered pattern to homogeneous pattern.

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ABSTRACT (IN KOREAN)

돼지 관상동맥에 일반 금속 스텐트와 에버롤리무스 용출 스텐트를 삽입 한 후 혈관내 광단층영상을 이용한 신생내막의 연속적인 변화 관찰 연구

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목적 광단층영상(optical coherence tomography)을 이용하여 정상 돼지 관상동맥에 삽입된 에버롤리무스 용출 스텐트 (everolimus-eluting stent)와 일반 금속 스텐트(bare metal stent)의 연속적인 신생내막 조직의 변화를 알아보고자 하였다.

배경 현재까지 광단층영상을 이용한 약물 용출성 스텐트의 연속적인 신생내막 조직의 변화에 대해서는 충분히 연구가 되지 않았다.

방법 15마리의 정상인 돼지의 관상동맥에 15개의 일반 금속 스텐트와 15개의 에버롤리무스 용출 스텐트 치료를 시행한 후에 1, 3, 6개월 후에 연속적인 관상동맥 내 광단층영상을 시행하였다. 1개월째 추적 검사상 스텐트 구간내 신생내막의 생성으로 단면적이 최대로 협착 된 부분에서

정성적이고 정량적으로 신생내막의 변화를 연속적으로 조사하였다.

결과 일반 금속 스텐트가 삽입된 병변에서, 신생내막의 부피는 1, 3, 6개월의 추적검사에서 각각 6.5 (사분위 범위 4.7-7.6) mm^3, 6.9 (사분위 범위 4.6-8.2) mm^3, 6.4 (사분위 범위 4.3-7.4) mm^3으로 유의한 변화는 없었다 (p=0.882). 1, 3, 6개월째에 신생내막은 층화 패턴은 감소되는 양상 (각각 20.0%, 6.7%와 0%)을 보였지만 주로 균일한 패턴을 주로 보였다 (80.0%, 93.3%와 100%). 반면, 에버롤리무스 용출 스텐트가 삽입된 병변에서는, 신생내막 부피는 1에서 3개월 사이에서는 4.8 (사분위 범위 4.1-7.6) mm^3에서 9.8 (사분위 범위 5.7-15.1) mm^3으로 증가하였지만 (p<0.001), 3에서 6개월 사이에는 8.6 (사분위 범위 6.0-11..2) mm^3으로 유의하게 감소하였다 (p=0.007). 1에서 3개월 사이에는 신생내막의 층화 패턴은 26.7%에서 66.7%로 증가하였으나, 3에서 6개월 사이에는 20.0%까지 감소하였다.

결론 본 동물 모델의 광단층영상을 이용한 연구에서 에버롤리무스 용출 스텐트는 신생 내막의 조직 특성이 변화하면서 동시에 신생내막의 부피는 이중 패턴의 변화가 생긴다는 것을 보여주었다.

핵심되는 말 : 신생내막, 광단층영상, 약물용출성스텐트