# Assessment Technical Feasibility and Bio-compatibility of a Newly Designed Separate Type Stent-Graft in the Normal Canine Aorta

Young-Cheol Weon

Department of Medicine

The Graduate School, Yonsei University

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Directed by Professor Do Yun Lee, M.D. PhD.

The Master's Thesis submitted to the Department of Medicine the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

Young-Cheol Weon

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This certifies that the Master's Thesis of Young-Cheol Weon is approved

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Thesis Supervisor: Do Yun Lee, M.D. PhD.

_____

Thesis Committee Member#1: Nam Sik Chung, M.D. PhD.

_____

Thesis Committee Member#2: Sung-Gwon Kang, M.D. PhD.

The Graduate School

Yonsei University

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# Assessment Technical Feasibility and Bio-compatibility of a Newly Designed Separate Type Stent-Graft in the Normal Canine Aorta

Young-Cheol Weon

*Department of Medicine*
*The Graduate School, Yonsei University*
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Purpose: The objectives of this study were to assess the performance of a newly designed separate ultra-thin polyester fabric stent-graft system with respect to the technical feasibility of transfemoral deployment, the maintenance of vessel patency, the deformity of stent due to mechanical defect and to evaluate in vivo healing characteristics including thrombus formation, endothelial covering of the stent-graft when placed in the normal aorta of the canine model.

Methods: Nine separate type stent-grafts were placed in the proximal descending thoracic aorta of nine dogs and evaluated at 4 (n=2), 6 (n=2),

8(n=2), and 12 (n=3) weeks. The assessment of patency of the stent-graft was done using angiography prior to euthanasia. Using a digital camera attached on the stereoscopy, thrombus and endothelial formation were evaluated and the quantification of the endothelial formation was measured by electron microscopy. Thickness of the neointima and inflammatory cell infiltration were also measured.

Results: Transfemoral deployment of a separate type stent-graft was successful and free of complications in all nine dogs. There was no stent-graft migration or deformity during stent-graft placement and follow-up period of 12 weeks. Angiographically, just prior to euthanasia, 9 of nine aortic stents were patent. Histologically, endothelialization on the surface of the stent-grafts started from 4 weeks and completely covered with neointima in 12 weeks. The neointima was very thin (less than 1mm) and regular and there was no hyper-proliferation that can disturb the flow of the aorta in all cases.

Conclusion: The separate type stent-graft deployed easily and achieving accurate deployment without migration. This animal study provided an examination of the healing process associated with the ultra-thin polyester

fabric nitinol stent and demonstrated predictable healing characteristics in normal thoracic aorta in canine model.

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key words : stent-graft, animal, aorta, nitinol stent, endothelialization

# Assessment Technical Feasibility and Bio-compatibility of a Newly Designed Separate Type Stent Graft in the Normal Canine Aorta

Young-Cheol Weon

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## I. INTRODUCTION

Thoracic aortic aneurysms and dissections are life-threatening conditions and pose a significant challenge for treatment. The incidence of thoracic aortic aneurysms is approximately 6 per 100,000 persons per year[1]. For thoracic aortic aneurysms, surgical repair with prosthetic graft is the traditional therapy with operative mortalities of 5−20% [2]. It is also associated with substantial morbidity such as postoperative paraplegia, renal failure and need for prolonged ventilator support[2,3]. Aortic dissection is also one of the most common non-traumatic aortic pathologic conditions with the annual incidence

of 10–20 cases per million people per year that exceeds the incidence of spontaneous rupture of aortic aneurysms[4]. Acute aortic dissection or aneurysms may be treated conservatively, but emergency surgery is often necessary when the risk of rupture is high and organ ischemia is marked. For alternatives of surgical treatment for aneurysms and dissections of thoracic aorta, variable endovascular techniques and many types of endovascular stents and grafts have been developed for more than 10 years[4-12].

Most of the current endovascular stent-grafts developed for treatment of thoracic aneurysms and dissection, however, have many limitations including the restriction in the range of suitable anatomy and the need to be placed with a large guidance delivery system that necessitates surgical cut down in the femoral artery[11-15]. For these reason, we newly devised a separate type ultra-thin polyester fabric stent-graft system to provide a less invasive and more feasible technique, to decrease complication and more over to provide possible percutaneous approach by reducing the introducer profile for the case with small ilio-femoral artery or tortuous iliac artery[16]. The reduced profile of the device allows introduction of the stent through a 10-F introducing system with 12-F femoral sheath, while the special design minimizes stent-graft movement during deployment.

The objectives of this study were to assess the performance of a newly designed separate ultra-thin polyester fabric stent-graft system with respect to the technical feasibility of transfemoral deployment, the maintenance of vessel patency, the deformity of stent due to mechanical defect and to evaluate in vivo healing characteristics including the thrombus formation, endothelial covering of the stent-graft when placed in the normal aorta of the canine model.

# II. MATERIALS AND METHODS

## 1. Animals

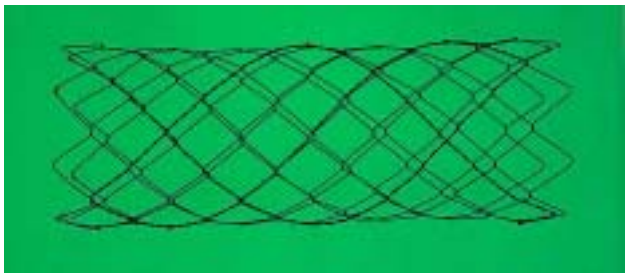
In compliance with the Guide for the Care and Use of Laboratory Animals (NIH Publication 86-53, revised 1985), 9 adult mongrel male dogs (20 - 30 Kg: mean 25 Kg) were housed and maintained in facilities approved by the American Association for the Accreditation of Laboratory Animal Care. Animals were fed a normal laboratory diet and water. Arterial access was obtained by cut-down on the right femoral artery under a general anesthesia (sodium pentobarbital, 30 mg/Kg). After procedure, animals continued on a normal diet. The dogs were sacrificed by exsanguinations under deep sodium pentobarbital anesthesia after follow-up of 4 weeks (group 1, n=2), 6 weeks (group 2, n=2), 8 weeks (group 3, n=2), and 12 weeks (group 4, n=3), respectively.

## 2. Construction of the Separate Stent-Graft

The separate type stent-graft systems were handmade in our research laboratory (S & G Biotech Inc, Seoul, Korea) and consisted of two parts: a outer graft-stent and an inner bare stent (Fig1).

Fig 1. Components of the separate stent-graft (34 mm × 10 cm). The outer graft-stent consisted of three parts: a proximal stent, a graft made of synthetic ultra-thin polyester textile fabric, and a distal stent (A). The Inner bare stent (B) was knitted from a single thread of 0.3-mm nitinol wire in a tubular configuration without the interlocking pattern. Assembled separate stent-graft (C); the graft is fully expanded by the inner bare stent.

A



B

C

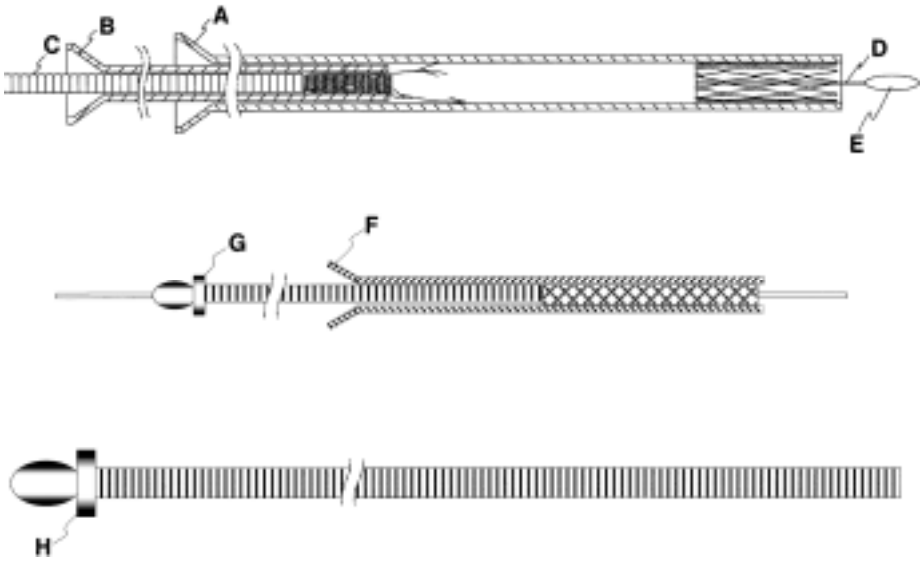
The outer graft-stent consisted of three parts: a proximal stent, a graft made of synthetic ultra-thin polyester textile fabric (MiKwang, Taegu, Korea), and a distal stent. The synthetic polyester graft was attached to two different types of stents. The thickness of polyester graft, used in this study, was less than 100 microns. The proximal and distal stents were knitted and wound from a single thread of 0.245 mm nitinol wire in a tubular configuration without interlocking diamond-shaped pattern. The proximal and distal stents were 20 mm in diameter and 14 mm long. The three parts of the stent-grafts were tied with blue monofilament (4-0 Prolene; Ailee, Pusan, Korea) by using a tapered needle. The two stents were each separated by 0.5 cm from a segment covered by the synthetic polyester. The synthetic polyester was 20 mm in diameter and 5 cm long. Gold radio-opaque markers were attached at both ends of proximal, distal, and inner bare stents to enhance visibility of stent-graft under fluoroscopy.

3. Deployment Technique

The separate stent-grafts were introduced through a 12-F femoral sheath (S & G Biotech Inc, Seoul, Korea). The introducing system consisted of four

parts: a 10-F outer sheath made of braided tube (S & G Biotech Inc, Seoul, Korea), a coil pusher (outer diameter of 2.22 mm, inner diameter of 1.5 mm), and a 4-F catheter as a guide wire passing tube (Fig 2) [16]. The separate type stent-grafts, outer graft-stents and inner bare stents, were preloaded into the 10-F introducing system. After deployment, the outer graft-stent was centrally supported by a coaxial inner bare stent.

Fig 2. Diagram of the components of the introducing system for the separating stent-graft: *A*, 10-F synthetic resin sheath; *B*, synthetic resin pusher; *C*, coil pusher; *D*, guide wire passes the tube; *E*, olive tip; F, loader for inner bare stent; *G*, loader pusher; and *H*, pusher for inner bare stent. (Reprint with permission from Kang et al.[16])



After each dog was given a general anesthesia (sodium pentobarbital, 30 mg/Kg), a 12-French short vascular sheath was inserted through right femoral artery with cut down. Pigtail shaped angiographic catheter (COOK, Bloomington, Ind. USA) was advanced to ascending aorta and aortogram was performed. After aortic angiogram, stiff guide wire was advanced through angiographic catheter to ascending aorta, and the angiographic catheter was removed. After systemic heparin (100U/Kg) was given, the introductory system was advanced over the guide wire under fluoroscopic monitoring into the proximal descending thoracic aorta, just distal to the origin of left subclavian artery. The graft-stent was deployed at proximal descending thoracic aorta. After deployment of graft-stent, all introductory system, including outer sheath, pusher, and guide wire passing tube, was removed, but guide wire remained in aorta. Second introductory system containing inner bare stent was advanced over the guide wire, and inner bare stent was deployed inside of the outer graft-stent. Two stents in graft-stent and inner bare stent were overlapped about 1cm.

Angiography was performed immediately after stent placement to evaluate stent-graft position and the patency of the stent-graft. Follow-up Angiography were obtained at the end of each follow-up period. No

anticoagulant or anti-platelet agents were administered after stent-graft placement. Blood sampling for CBC and ESR were performed once in a week.

4. Assessment of Stent thrombosis and neointimal formation

A complete necropsy was performed, and grossly examined the stomach, intestine, liver, spleen, and kidneys to evaluate any evidence of ischemic change or infarction of these solid organs. After the vessels containing the grafts were removed, thrombus and endothelial formation were evaluated using a digital camera attached on the stereoscopy. The quantification of the endothelial formation was measured by electron microscopy. Thickness of the neointima and inflammatory cell infiltration were also measured.

# III. RESULTS

Transfemoral deployment of a separate stent-graft was successful and free of complications in all nine dogs. Visibility of the separate stent-graft was excellent owing to the gold markers that were attached at both ends of the stents. The 10-F introducing system was advanced easily to the thoracic aorta and the mean time required to place the separate stent-graft (defined as the time from pre placement aortography to the time of immediate post placement aortography) was 20 minutes.

Except two cases in 8 weeks and 12 weeks groups that showed slightly increased WBC count, all cases had normal WBC count during follow-up. RBC and Hb/Hct count were normal range. Platelet count was slightly decreased in all groups without any internal hemorrhage or other associated complications. Only one case in 12 weeks group had increased ESR in 2 weeks follow-up and normalized after then.

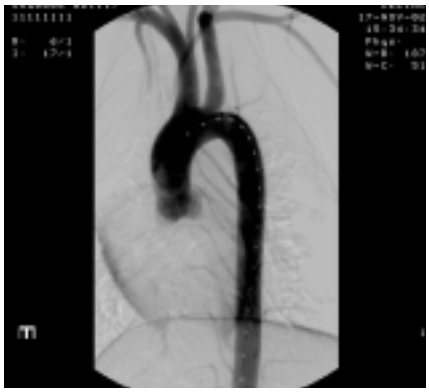
The angiograms obtained before, just after and 4 weeks (n=2), 6 weeks (n=2), 8 weeks (n=2), and 12 (n=3) after stent-graft placement. There was no migration or deformity of the stent-graft during deployment or follow-up period of 12 weeks. All stent-grafts were patent at angiogram that was obtained before sacrifice.

On the gross examination for looking evidences suggesting ischemic change or infarction of the intestine and solid organs including liver, spleen, kidney and stomach, there was no abnormality except in one dog that have a kidney with wedge shaped discoloration, probable ischemia or infarction, at the apex. But the relationship to the procedure or stent-graft could not be evaluated.

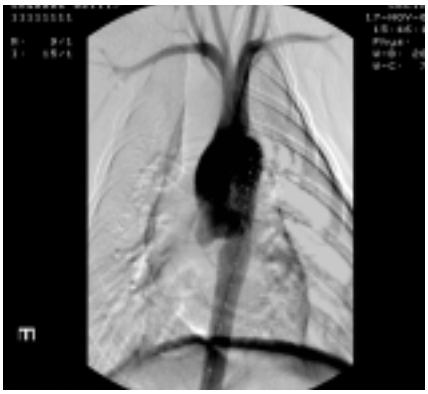
On the pathologic examination, endothelialization on the surface of the stent-grafts started from 4 weeks and completely covered in 12 weeks neointima (Fig 3).

The neointima was very thin (less than 1mm) and regular. No hyper-proliferation can disturb the flow of the aorta was seen in all cases. The aorta where the stent-graft was located has mild inflammation in 4 weeks and normalized during follow up. There was no thrombus between the stent-graft and the aorta suggesting the stent-graft stop the flow completely. In one case of 4-week group, focal intimal hyperplasia was seen at the distal part of stent-graft. This did not influence on the blood flow and, we could find very thin and even neointimal cell layer and smooth muscle cell layer in the other part. There was a case with small focal hemorrhage at the aortic wall at the junction between grafts and distal stent in a 4-week group (Fig 4).

Fig 3. Three angiograms obtained before (A), just after (B) and in 12-week after stent-graft placement (C), in a case of 12-week follow-up group. The stent is intact without any deformity or migration at the follow-up angiogram. The transparent neointima covers all stent-grafts, The neointima was very thin (less than 1mm) and regular on the gross (D) and microscopic examination (E).



A



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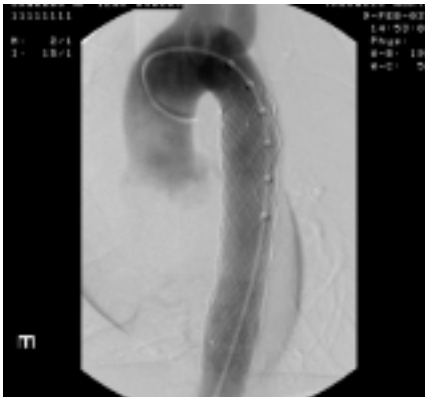
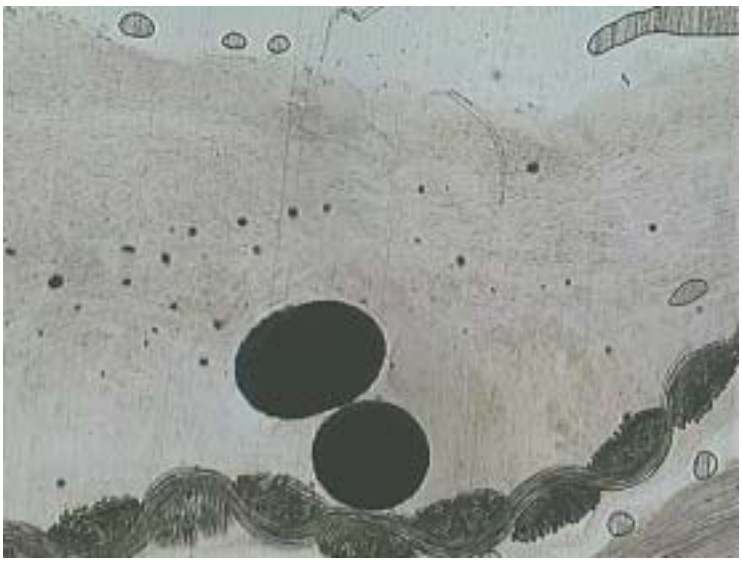


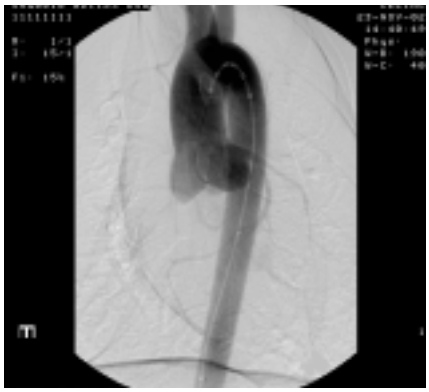
C

D

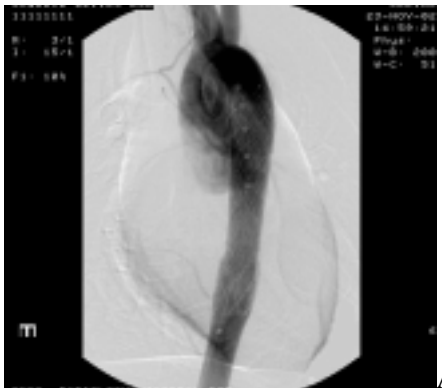


E

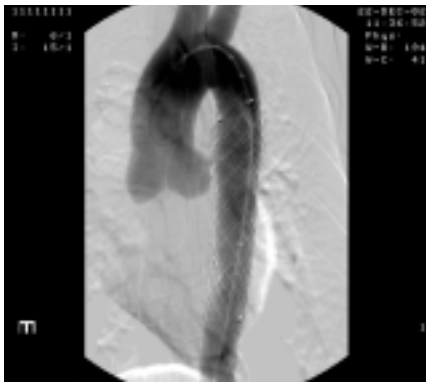
Fig 4. Three angiograms obtained before (A), just after (B) and in 4-week after stent-graft placement in a case of 4-week follw-up group (C). Focal narrowing is present at the distal part of the stent. On the gross examination (D), dark brown hematoma is present in this distal part of stent-graft. Microscopic examination (E) at the site of focal hematoma shows thin intimal cell layer, sub-intimal hematoma, and proliferation of smooth muscle cell. In the other part, very thin regular neointimal cell layer and smooth muscle cell layer are seen.



A

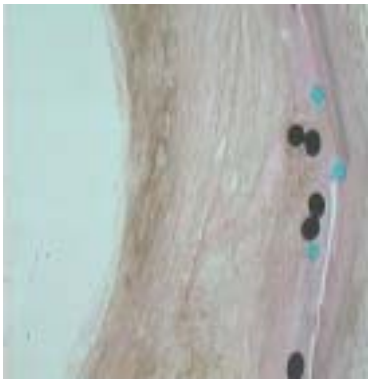


B



C

D



E

It was expected that stent struts would themselves scrape the endothelial layer during expansion. The intimal thickness of each group was measured on both stent wire and graft (Table 1). The intimal thickness increased gradually on the duration of follow-up period.

Table 1. The intimal thickness of each groups.

| Group | Intimal thickness (mm) | |
|---|---|---|
| | Stent* | Graft** |
| 4 weeks- group | 0.213 | 0.157 |
| 6 weeks-group | 0.326 | 0.177 |
| 8 weeks-group | 0.538 | 0.208 |
| 12 weeks-group | 0.637 | 0.761 |

* Stent: Thickness between stent surface and innermost luminal surface

**Graft: Thickness between graft surface and innermost luminal surface

# IV. DISCUSSION

The treatment paradigms of aortic aneurysm and aortic dissection have evolved with the development of new endovascular tools and the better understanding of the pathophysiology of this disease. For thoracic aortic dissections, the primary treatment is usually medical therapy consisting of b-blockade, anti-hypertensive therapy, and general supportive measures. Although surgical intervention with graft interposition is the traditional treatment for most patients with diseases of the descending aorta[17], the technique of endoluminal aortic stent-graft placement has recently been introduced for repair of abdominal and thoracic aneurysms[18-20] and endoluminal repair is a new therapeutic alternative which is yielding encouraging results in the high-risk setting of aortic dissection[15, 21]. Treatment strategy for type-B dissection is exclusion of the primary entry tear in order to induce thrombosis and retraction of the thoracic false lumen. Placement of a stent-graft across the primary entry tear could be an effective single-step treatment that may be more efficient than endovascular techniques for the relief of ischemic complications and less invasive than aortic graft replacement at thoracotomy[15, 21, 22]. Further more, stent-graft placement create a remodeling of the aorta by expansion of the true lumen and

thrombosis and retraction of the false lumen, which mimics the natural healing process of the aorta[15]. Thus, Stent-grafting techniques hold tremendous promise for the high-risk patient, but several limitations should be discussed: including the biocompatibility of used material, proper device fixation, stent-graft migration and alteration in the shape and structure of the grafts, and the healing performance of the stent-graft.

The technical feasibility and the biocompatibility of the device have an important role in technical and clinical success of endoluminal repair. Many doubts have prompted the completion of experimental trials and feasibility studies before new devices are used in clinical practice. In our study, transfemoral deployment of a separate type stent-graft was successful in all nine dogs with free of complications. We found that they could be introduced reliably into the thoracic aorta and deployed in a standard fashion that is familiar to most interventionists. With the 12-F sheath, the 10-F introducing system was advanced easily to the thoracic aorta and the mean time required to place the separate stent-graft was acceptable. The separate stent-graft for aortic dissection offers several advantages: (*a*) Surgical aortotomy may not needed, (*b*) blood pressure control is not required during deployment, (*c*) the stent-graft does not migrate during deployment, and (*d*) the procedure time is relatively short (about 20 min in this study). Once deployed, the self-expanding,

polyester-covered stents did not exhibit recoil, nor did they appear to induce acute thrombus formation or trauma to vessel walls. Further more 10-F introducing system is more flexible than the other larger introducing systems, therefore, the separate stent-graft could be more easily used in patients who have tortuous or narrow iliac vessels. The gold markers that were attached at both ends of the stents facilitated fluoroscopic visualization and precise deployment of the stent-grafts. This would contribute satisfactory exclusion of the entry zone without proximal or distal endoleaks in a case of aortic dissection.

Structurally, the stent-graft displayed no instability or disintegration, such as suture breaks, displacement of the knitted wire elements, wire fractures, or tears in the polyester sleeve over the 12 weeks of implantation. Successful endovascular treatment of aortic diseases requires good proximal fixation to avoid migration and proximal graft-related endoleaks. A number of factors come into play, environmental factors such as the shape and length of the proximal neck, the morphology of the arotic wall, the presence of thrombus and the characteristics of the stent-graft itself such as the radial force and size of the stent-graft, the type of device (self-expanding versus balloon expandable), and the presence of proximal hooks or barbs. In our device, the separate type stent graft can be avoid migration during deployment and using

the inner bare stent as a supporting skeleton positioned after deployment of the graft, the profile of the stent-graft could be further reduced, allowing patients with smaller iliac arteries to be considered for treatment. Such a sequentially constructed stent-graft system can provide the lower profile and strength required. It also provides excellent longitudinal flexibility, enabling the system to pass through an extremely tortuous iliac artery, increasing the technical success rate. The radial force in a modular stent-graft system such as ours is based on a flexible and powerful inner stent. Our device has 2 design features that limit migration potential: barbs on the proximal stent and a 0.5 cm gap between proximal stent and Dacron graft for the diseased part of the aorta. Antegrade aortic flow is also maintained through the gap during stent-graft deployment and blood pressure control is not required during deployment.

Histologically, the ultra-thin polyester fabric-covered stents demonstrated predictable healing. On the pathologic examination, endothelialization on the surface of the stent-grafts started from 4 weeks and completely covered in 12 weeks neointima on this study. The new endoluminal surface was covered by a confluent very thin (less than 1mm) monolayer of mature endothelial cells. The healing of the luminal surface gave way to the development of a neointima - thin internal collagenous capsule with a continuous endothelial

lining. The neointima was composed primarily of collagen, elastic fibers, and variable numbers of poliferative-synthetic smooth muscle cells. Contact between either the polyester sleeve or the nitinol stent and the aortic wall induced no tissue necrosis, and the nitinol wire was well incorporated within the collagenous tissue. The overall inflammatory response was minimal, with no evidence of histiocytes within the neointima, media, and adventitia. After 12 weeks, no inflammatory cells were observed in contact with the nitinol stent. In general, this illustrates the favorable biocompatibility that is typical of this foreign material[23-26]. Using ultra-thin polyester, even though endothelialization at the area of graft is slightly slow that at the area of stent, the degree and nature of the intimal thickening observed in our study supports previously reported studies, where the use of covered stents compared with non-covered stents, provided a stronger, but not an absolute, barrier for blocking the migration and/or proliferation of intimal and medial cells associated with hyperplasia and stenosis[27-32]. One case of 4 week had more proliferation of the intima at the periphery of the distal stent, but no hyper-proliferation can disturb the flow of the aorta was seen in all cases. There is a case with small focal hemorrhage at the aortic wall at the junction between graft and distal stent in a 4-week group (Fig 4). The mechanism of endothelial injury during stent expansion is not clear. Contributing factors to endothelial

injury during stent expansion may include balloon-vessel contact between struts; pressure imposed by blood confined to the closed space between balloon, stent struts, and vessel wall during expansion; inhomogeneous circumferential strain applied to the vessel wall during dilation; or acute alterations in flow. The reproducible localization of endothelial cell loss to stent interstices also implies that factors such as balloon pressure and compliance, strut thickness and configuration, speed of inflation, and vessel over sizing may all be important determinants of endothelial loss[33]. We did not use balloon for stenting in our series and it was expected that stent struts would themselves scrape the endothelial layer during expansion.

Many authors reported the results of animal study with various stent-graft systems. But, to our knowledge, this is the first report of animal study with ultra-thin Dacron graft. This animal study has provided an examination of the healing process associated with the ultra-thin polyester fabric and nitinol stent. However, the healing process and pattern of endothelialization of aneurismal model is different from normal thoracic aorta. Hence, further studies in aneurysm or dissection model are required to elucidate healing process of nitinol-ultra-thin Dacron devices in such diseased aorta.

# V. CONCLUSION

The technique of endoluminal aortic stent-graft placement has recently been introduced for repair of abdominal and thoracic aneurysms and endoluminal repair is a new therapeutic alternative that is yielding encouraging results in the high-risk setting of aortic dissection.

The newly designed separate type stent-graft can be deployed easily without the need for blood pressure reduction, achieving accurate deployment without migration in normal thoracic aorta of canine model. For it's low profile, the separate stent-graft could be more easily used in patients who have tortuous or narrow iliac vessels. This animal study has also provided an examination of the healing process associated with the ultra-thin polyester fabric nitinol-stent and demonstrated predictable healing characteristics in normal thoracic aorta.

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Abstract (국문 요약)

# 정상 흉부 대동맥에 분리형 스텐트-그라프트 설치후 추적 결과: 잡견에서의 실험적 연구

< 지도교수 이 도 연>

연세대학교 대학원 의학과

원 영 철

동맥류와 대동맥박리는 국내에서 그 빈도가 증가하는 질환으로 이에 대한 고식적 치료법은 개복이나 개흉 수술로 병변 부위의 대동맥을 절개하고 인조혈관으로 이어주는 것이었다. 최근 스텐트에 인조혈관을 부착한 스텐트-그라프트가 개발되어 개흉술이나 개복술 없이 대퇴동맥을 통하여 병변 부위에 인조혈관을 설치하는 것이 가능해졌다. 이 시술에 사용되는 스텐트-그라프트의 대부분이 외국 제품이며, 굵기가 6-8 mm 의 범위로 대퇴동맥을 수술적으로 박리하여 절개하여야 시술이 가능하고, 설치 도중 혈류에 의한 이동을 방지하기 위해 혈압을 낮추거나 심장 박동을 멈추어야 하는 단점이 있었다. 최근 국내에서 굵기가 4mm 에 불과하여 경피적으로 시술이 가능하고 설치 중 혈류를 차단하지 않아 혈압의 조절이 불필요한 분리형 스텐트-그라프트가 개발되었다. 본 연구는 이

분리형 대동맥 스텐트-그라프트를 실험동물의 정상 흉부대동맥에 설치하는 과정이 사용법에 따라 시술할 때 항상 원하는 부위에 안전하게 설치되는지, 설치한 뒤 위치의 이동이 발생하는지 여부와 3 개월 동안의 추적 기간동안 스텐트-그라프트의 기계적 결함에 의한 변형, 혈전 형성 및 혈관내피세포로 덮히는 정도를 평가하고자 하였다.

잡견 9 마리에 스텐트-그라프트를 우측 대퇴 동맥을 통해 하행 흉부 대동맥에 설치하고, 4 주(n=2), 6 주(n=2), 8 주(n=2), 12 주(n=3)군으로 나누어 희생한후 스텐트-그라프트 설치에 따른 문제점 (목표한 위치에 정확히 설치되는 지, 설치 도중 혈류에 의한 이동이 발생하는지, 등)의 유무, 디지털 감산 혈관조영술을 시행하여 스텐트-그라프트의 위치와 스텐트-그라프트를 통한 혈류에 대한 평가, 혈전 형성 여부와 내막 형성의 정도를 평가하였다.

경피적 분리형 스텐트-그라프트는 아홉 마리 모두에서 합병증 없이 성공적으로 시술 되었다. 설치 도중 또는 12 주간의 추적 검사 중 혈류에 의한 이동이나, 변형은 없었다. 디지털 감산 혈관조영술에서 모든 스텐트의 개통성은 양호 하였으며, 조직학 검사상 내막은 4 주에 시작하여 12 주에 완전히 스텐트-그라프트를 덮었다. 내막은 아주 얇고 (1 mm 이하) 규칙적이었으며, 혈류를 막을 정도의 혈전은 형성되지 않았다.

본 실험의 결과 국내에서 새로 개발된 경피적 분리형 스텐트-그라프트는 실험동물에 설치하는데 용이 하였다. 12 주의 추적기간중 스텐트-그라프트의 이동 혹은 변형이 보이지 않았으며, 스텐트-그라프트를 통한 혈류는 잘 유지 되었고, 설치한 부위의 대동맥에 이상 조직 반응을 보이지 않았다. 조직병리 검사에서는 스텐트 그라프트 내부는 신생내막이 잘 형성되어 있었고, 신생내막의 이상증식을 보이지 않았으며 임상용으로 안전하고 효과적으로 사용될 수 있을 것으로 사료된다.

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핵심 되는 말 : 스텐트-그라프트, 동물, 대동맥, 니티놀 스텐트, 내막 형성