의학박사 학위논문

‘노터치’ 방법으로 획득한 복재정맥을 관상동맥 우회로술에서 제 2 도관으로 사용할 때 복재정맥의 채취 부위에 따른 무작위배정 비교

: 면역조직화학 분석 및 1 년 추적 조영술 결과

A Randomized Comparison of ‘No-Touch’ Harvested Upper versus Lower Leg Saphenous Vein as a Secondary Conduit for Coronary Artery Bypass Grafting

: Immunohistochemical analyses and 1-year follow-up angiography

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Thoracic and Cardiovascular Surgery, Medicine

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A Randomized Comparison of 'No-Touch' Harvested Upper versus Lower Leg Saphenous Vein as a Secondary Conduit for Coronary Artery Bypass Grafting

: Immunohistochemical analyses and 1-year follow-up angiography

by

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Abstract

A Randomized Comparison of 'No-Touch' Harvested Upper versus Lower Leg Saphenous Vein as a Secondary Conduit for Coronary Artery Bypass Grafting

: Immunohistochemical analyses and 1-year follow-up angiography

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Background: Although total arterial revascularization is known to have the best long-term outcomes in coronary artery bypass grafting (CABG), saphenous vein grafts (SVGs) are most frequently used as a second conduit for CABG because they are convenient to harvest and plentiful. In an effort to improve the outcomes of using SVGs in CABG, we compared the histopathology and 1-year angiographic change of SVGs that were harvested from either the upper or the lower leg.

Patients and methods: Patients aged 40-75 years old who were undergoing off-pump CABG for multi-vessel coronary artery disease were enrolled. A

total of 26 patients were randomized into the following 2 groups: an upper leg vein (ULV) group (n=13) and a lower leg vein (LLV) group (n=13). All of the SVGs were harvested using the 'No-Touch' technique, preserving perivascular tissue. Pressure dilatation was not applied. Before Y-anastomosis to the left internal thoracic artery, small segments of the 'proximal' and 'distal' ends of the SVG were obtained, and another segment, which had been exposed to internal thoracic arterial pressure before final anastomosis, was sampled ('dilated'). These three samples were histopathologically analyzed and subjected to hematoxylin and eosin, Kruppel-like factor (KLF)-4, serum response factor (SRF), and myocardin staining. Endothelial integrity, expression of vascular smooth muscle cell (VSMC), activation of related proteins and preservation of medial smooth muscle folding were measured, and luminal diameter/intimal and medial thickness were measured. Coronary angiography (CAG) was performed postoperatively and at 1 year after CABG. The SVG diameter and filling frame counts were measured by CAG to evaluate vascular remodeling.

Results: No significant differences in endothelial integrity, expression of VSMC activation-related proteins and preservation of smooth muscle folding were observed between the ULV and LLV groups. The 'dilated' sample, which was initially adjacent to the 'proximal' sample, had a

significantly larger luminal diameter in both groups (ULV group: dilated [1477±353 μm] *vs* proximal [858±266 μm], *P*<0.001; LLV group: dilated [1138±419 μm] *vs* proximal [623±143 μm], *P*=0.003). Additionally, the 'dilated' samples had thinner intima than the 'proximal' samples in both groups, as follows: the ULV group (dilated [132±124 μm] *vs* proximal [218±114 μm], *P*=0.036) and the LLV group (dilated [67±52 μm] *vs* proximal [175±61 μm], *P*<0.001). However, significant between-group differences did not exist. Twenty-four patients (92%) underwent a 1-year CAG, and it revealed that the diameter of SVGs decreased during the first year (negative remodeling) on average, as follows: ULV group (postoperative [4.6±0.8 mm] *vs* 1-year [3.5±1.6 mm], *P*=0.012) and LLV group (postoperative [4.1±0.8 mm] *vs* 1-year [2.5±1.1 mm], *P*=0.001). However, the decrease in the SVG diameter did not show a significant difference between groups (analysis of covariance, *P*=0.210). A total of 2 patients (8%) showed SVG occlusion at 1-year CAG: 1 of 12 (8%) in the ULV group and 1 of 12 (8%) in the LLV group (*P*>0.999). The SVG filling frame count decreased during the first year after CABG in both groups, without between-group differences (analysis of covariance, *P*=0.529).

Conclusion: No clear evidence of superiority could be found with regard to the harvest site. ULV and LLV showed similar histopathology and

angiographic changes during the first year. Further studies are needed to evaluate the long-term changes in SVGs as a secondary conduit in CABG.

ClinicalTrials.gov ID: NCT01974492

Keywords: saphenous vein, coronary artery bypass grafting, anatomy, patency

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List of Abbreviations

ANCOVA	analysis of covariance
CABG	coronary artery bypass grafting
CAG	coronary angiography
H&E	hematoxylin and eosin
ITA	internal thoracic artery
KLF4	Kruppel-like factor 4
LITA	left internal thoracic artery
LLV	lower leg vein
SAVERITA	Saphenous Vein Versus Right Internal Thoracic Artery as a Y-Composite Graft
SRF	serum response factor
SVG	saphenous vein graft
SYNTAX	Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery
ULV	upper leg vein
VSMC	vascular smooth muscle cell

1. Introduction

Since the world's first revascularization of the stenotic left anterior descending artery with a direct anastomosis technique using the internal thoracic artery (ITA) by Vasilli Kolesov in 1964 (1), coronary artery bypass grafting (CABG) has been performed for over 40 years (2). CABG in the initial period always required cardiopulmonary bypass support (conventional CABG). Anastomoses were performed on an arrested heart. However, substantially high perioperative mortality was a problem in that period. Follette and Buckberg showed the harmful effects of cardioplegic arrest without modern style cardioplegia and consequent myocardial ischemic insult during CABG (3). These findings inspired research into reducing myocardial ischemic injury during cardioplegic arrest. Potassium-rich cardioplegia with metabolic substrates, which was introduced in the 1970s, brought enormous improvement in the outcomes of CABG (4).

Saphenous vein grafts (SVGs) were the most frequently used conduit for CABG in the 1970s (5). In the literature, SVGs were used in 87% of CABG procedures performed in 1979 (United States) (6). However, the patency of SVGs was shown to be poor by FitzGibbon and colleagues in 1978 (11%

occlusion rate during 2-3 weeks postoperatively) (7). Other reports that had similar conclusions followed (8-11). Graft thrombosis was believed to be the cause of early SVG failure, and the mechanism of late failure was explained by intimal hyperplasia and atherosclerotic changes (12).

Because of the inferior long-term patency with SVGs, the internal thoracic artery (ITA), which had been used in the world's first CABG, was considered to be the best conduit available. A report from the Cleveland Clinic showed better patency and long-term survival with ITA to left anterior descending artery bypass than with SVG-only CABG (13). Additionally, the use of bilateral ITAs showed even better results than single ITA grafting in terms of reoperation and long-term mortality (14, 15).

With the invention of the Octopus stabilizer in 1996, the technical difficulty in performing off-pump CABG was greatly reduced, and off-pump CABG became a widespread operative technique (16). To maximize the benefits (lower stroke risk) of not cannulating the aorta in off-pump CABG, the concept of 'anaortic' CABG was introduced. Comparison between clampless (anaortic) off-pump and conventional CABG showed significant reductions in the rates of death and stroke with off-pump CABG (17). Moreover, the absence of aortic manipulation was related to significantly

lower neurological complication rates in a meta-analysis of 11,398 patients (18).

Because anaortic CABG excludes proximal graft anastomosis to the ascending aorta, the graft strategy is limited. The two principal strategies are to use bilateral in situ ITAs or a single arterial source (left ITA) with a T- or Y-connected composite graft. For the latter case, there is no doubt that the left anterior descending artery should be revascularized with the in situ ITA (primary graft). However, the choice of secondary graft is controversial. Although total arterial revascularization is most often recommended according to the recent guidelines on CABG (19), the real-world practice does not comply with these guidelines. CABG with second arterial graft occupies a small proportion of the total number of CABG procedures: approximately 5% in the STS database (20), 26% in the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial registry (21), and 13% use of bilateral ITAs in a 2009 report of the Australasian Society of Cardiac Surgery (22).

A number of surgeons still use SVGs as a secondary conduit in CABG. This phenomenon is mainly attributable to the technical difficulty of ITA harvesting (especially skeletonization) and the increased risk of deep sternal

wound infection with bilateral ITA use (23). Moreover, harvesting of bilateral ITAs requires more time than harvesting the ITA and SVG simultaneously. We previously evaluated the efficacy of several secondary conduits before: the right internal thoracic artery, gastroepiploic artery, and SVGs (24-30). Much recent research has been undertaken to improve the long-term patency of SVGs as secondary grafts (31-35), and we recently have also been interested in this topic (36-39).

In the literature, the key elements in improving the outcomes with SVGs are preservation of endothelial integrity (36), avoiding mechanical and thermal injury during harvesting (31, 33, 34, 36), and leaving perivascular tissue with SVG (34, 35). These approaches constitute the concept of 'No-Touch' harvesting. With this 'No-Touch' SVG harvesting technique, we began a randomized, controlled trial (Saphenous Vein Versus Right Internal Thoracic Artery as a Y-Composite Graft [SAVE RITA]), in which the patency and clinical outcomes were compared between the free right ITA and a SVG as the secondary graft (37). The last paper on this trial showed equivalent 1-year patency and 4-year freedom from major adverse cardiac and cerebrovascular events (38). Our propensity score-matched comparison of 5-year graft patency and clinical outcomes in a total of 363 patients showed that CABG using SVGs had equivalent results to total arterial

revascularization (39).

From our extensive experience with strict follow-up angiography after CABG at postoperative day 1, 1 year, and 5 years (40, 41), we hypothesized that there would be differences in SVG remodeling and patency depending on harvest site. There has been a paucity of reports of the harvest sites of SVGs used in CABG (42, 43). The aim of this study was to evaluate the differences in SVGs harvested from either the upper or lower leg in terms of endothelial integrity, the expression of vascular smooth muscle cell (VSMC) activation-related proteins and remodeling over the first year.

2. Patients and Methods

From November 2013 to March 2014, a total of 26 patients were enrolled in this study. This study was designed as a randomized, controlled trial and was registered on Clinicaltrials.gov (NCT01974492) before the enrollment of the first patient. The institutional review board of Seoul National University Hospital approved this study (IRB No. 1308-077-514). Written informed consent was obtained from all of the study patients. The inclusion and exclusion criteria are shown in Table 1. Baseline patient characteristics are presented in Table 2. The sample size was calculated using PASS software, version 11 (NCSS, Kaysville, UT, USA). Values for sample size calculation were drawn from our previous research (36). The calculations were performed to evaluate the inequality in the degree of luminal staining. To achieve 82% power to detect a difference of 2.0 between the null hypothesis that both group means were 9.0 and the alternative hypothesis that the mean of group 2 was 7.0, with estimated group standard deviations of 1.7 and 1.7 and a significance level of 0.05 using a two-sided two-sample *t*-test, group sample sizes of 12 and 12 were necessary. Considering loss during follow-up, 13 patients were enrolled for each group: the upper leg

vein (ULV) and lower leg vein (LLV) groups. Block randomization was used, stratified by patient age (40-60 years old/61-75 years old) and sex. The table for randomization was provided by the Clinical Research Institute of Seoul National University Hospital. For eligible patients, a doctor who was not involved in this study informed the surgeon of the harvest site (upper or lower leg).

Operative techniques

Our techniques for surgery described in the previous study (36). Previously, we had harvested SVGs in a skeletonized manner with minimal manipulation. Skip incisions were preferred to reduce the risk of leg wound problems. Either thermal injury or mechanical stress during harvesting was strictly avoided. Maintaining this strategy, we adopted the lessons from the research of Souza DSR and colleagues (34), and we changed the technique of SVG harvesting immediately before the beginning of this study. Approximately 5 mm of width of the perivascular tissue on either side, including the vasa vasorum, was left attached to the SVG during harvesting (Figure 1). No manual intraluminal pressure dilatation was applied to the harvested SVG. This rule (No-Touch harvesting) was applied consistently in

all of the study patients regardless of harvest site. After harvesting the SVG, a Jackson-Pratt drain was placed in the harvest site, and the leg wound was closed immediately to avoid unexpected blood loss. This drain catheter in the SVG harvest site was removed when the amount of daily drained fluid was less than 10 cc. We obtained small (<1 cm) segments of the SVGs at the proximal and distal ends (Figure 2). The saphenous vein graft was then anastomosed in situ to the left ITA graft in the Y-composite manner. After the Y-composite graft was constructed, the distal end of the SVG was kept clamped with a plastic bulldog (Scanlan International Inc., St. Paul, MN, USA) during revascularization to the anterior and lateral wall. This technique was applied for passive dilatation of the SVG by the left ITA perfusion pressure. When the final length of the SVG that was needed to revascularize the last target vessel was determined, the bulldog clamp was released, and the small (<1 cm) segment of excess SVG was obtained. Therefore, 3 SVG samples were obtained from each patient; 'proximal', 'distal', and 'dilated'.

Histologic evaluation

The samples were fixed with 10% formalin solution in the operating room,

and the formalin-fixed samples were embedded in paraffin. The paraffin block was then sliced into 5-μm sections. For baseline evaluation, hematoxylin-eosin (H&E) staining was performed. Mouse monoclonal antibodies were used for immunohistochemistry: Kruppel-like factor (KLF)-4, serum response factor (SRF), and myocardin. These three molecules are known to regulate the change to a contractile phenotype (44). KLF4 suppresses the expression of multiple VSMC genes by both downregulating myocardin and preventing SRF/myocardin complexes from associating with VSMC gene promoters. Maintenance of smooth muscle folding is related to vascular compliance, which plays an important role in the future patency of SVGs. With myocardin staining, the degree of smooth muscle folding could be evaluated. To summarize, the following four types of staining were performed: endothelial integrity by (1) H&E staining; expression of VSMC-related molecules by (2) KLF4 and (3) SRF; and preservation of medial smooth muscle folding by (4) myocardin.

Ten-minute preincubation within 3% hydrogen peroxide in methanol was applied to block the endogenous peroxidase activity of the sections. To prevent background staining, the slices were then treated with 5% normal goat serum in Tris buffer solution at room temperature for 10 minutes. They were then treated with mouse monoclonal antibodies for KLF4, SRF, and

myocardin. The sections were rinsed, and horseradish peroxidase-conjugated secondary antibody was applied for 30 minutes. Then, these sections were stained with diaminobenzidine chromogen for 10 minutes and were counterstained with Mayer's hematoxylin for 15 seconds. The proportion of positive staining in the luminal circumference was measured, and the value (between 0 and 1) was rounded to two decimal places: endothelial staining (H&E, KLF4, and SRF) or preservation of smooth muscle folding (myocardin) (Figure 3). For analyses, a BX51 optical microscope (Olympus, Japan) was used. Luminal diameter and intimal and medial thicknesses were measured in the samples stained for myocardin, using a U-OCM10/100 eyepiece micrometer (Olympus, Japan) and a stage micrometer (Narika, Japan) (Figure 4).

Coronary angiography (CAG) follow-up

All of the patients underwent CAG follow-up on the first (mostly) or second postoperative day. One-year CAG follow-up was performed within 9-16 months from the initial surgery. Dual antiplatelet (aspirin + ticlopidine) therapy was most frequently used during follow-up. The flow velocity was measured using the frame count method; the number of CAG video frames

(1 frame = 1/15 sec) from the beginning to the end of the SVG filling was counted. The luminal diameter of the graft was proportionally calculated using the width of a 4 or 5 Fr (1.33 or 1.67 mm) CAG catheter as a reference. The diameter of the left ITA were measured at three points (2, 4, and 6 cm from the left ITA origin), and the average was used. The diameters of the SVG were measured in the same fashion (2, 4, and 6 cm from the Y anastomosis). The scientific image analysis software ImageJ (National Institute of Health, Bethesda, MD, USA) was used to measure length on 2 dimensional CAG captured images.

Statistical analysis

Statistical analyses were conducted at the Medical Research Collaboration Center in Seoul National University Hospital. SPSS software, version 20 (IBM, Armonk, NY, USA), and SAS software, version 9.3 (SAS Institute Inc., NC, USA), were used. For continuous variables, nonparametric tests (the Mann-Whitney U test and Wilcoxon's signed rank test) were used. For categorical variables, the Chi-square test, including Fisher's exact test, was used. To compare 1-year CAG results considering baseline (postoperative) CAG values, analysis of covariance (ANCOVA)

was used. A *P* value less than 0.05 was considered to show statistical significance.

3. Results

Baseline characteristics of the patients did not differ significantly between the ULV and LLV groups (Table 2). Number of revascularizations with SVG, SVG flow, and SVG to Y flow ratio showed no significant differences between the groups (Table 3). There was no significant difference in target vessel distribution between the groups. The Jackson Pratt drains were maintained for 8.1±7.5 days in the ULV group and 5.6±3.0 days in the LLV group (P=0.673).

Histopathologic analyses

In histopathologic analyses, the diameter of the SVG lumen and intimal and medial thicknesses were initially compared between groups (Table 4, Figure 5A, 4B, and 4C).

SVG luminal diameter on microscopy: The mean luminal diameters of the 'proximal', 'distal', and 'dilated' samples were 740±241, 652±180, and 1308±417 μm, respectively. Compared to the SVG luminal diameter, the diameter of the distal end did not differ significantly between the groups, but

the diameters of the proximal and dilated ends were significantly larger in the ULV group (Figure 5A). The proximal and dilated samples, which were adjacent to each other (Figure 2), showed the effects of passive dilation by left ITA pressure. In both groups, the dilated samples had significantly larger diameters than the proximal samples (intra-group pairwise comparison).

SVG intimal thickness on microscopy*:* The mean intimal thicknesses of the 'proximal', 'distal', and 'dilated' samples were 197±92, 156±62, and 100±99 μm, respectively. Intimal thickness showed no significant differences between the groups for the proximal, distal, or dilated end (Figure 5B). In contrast, in intra-group pairwise comparison, intimal thickness decreased significantly in both groups.

SVG medial thickness on microscopy*:* The mean medial thicknesses of the 'proximal', 'distal', and 'dilated' samples were 283±74, 287±75, and 254±79 μm, respectively. The medial thicknesses of the distal, proximal and dilated samples showed no significant differences between groups (Figure 5C). Even for the intra-group pairwise comparison, the change after passive dilation by the left ITA pressure was unclear.

The degree of endothelial integrity, expression of VSMC activation-related proteins, and preservation of medial smooth muscle folding are

presented in Table 5. Because the 'proximal' and 'dilated' ends were originally adjacent to each other, only these two types of samples were compared. No statistically significant differences were shown between the ULV and LLV groups. In contrast, intra-group pairwise comparison showed that there were significant decreases in the degree of endothelial integrity, expression of VSMC activation-related proteins, or preservation of medial smooth muscle folding in both groups.

CAG follow-up and clinical outcomes

Immediate postoperative CAG was performed in all of the study patients. A patient showed anastomosis site occlusion (SVG to obtuse marginal branch) on the immediate postoperative CAG, and she underwent reoperation on postoperative day 1. Her second postoperative angiography showed good patency at the initially occluded sites.

Twenty-four of 26 total study patients (92%) underwent 1-year follow-up angiography at 13±2 months. The 1-year changes in SVG filling frame counts and change in graft diameter are shown in Table 6 and Figures 6 and 7. The mean SVG filling frame count decreased during the first year in both groups: 31±12 (postoperative) vs 23±10 (1-year) frames (P=0.001).

However, the 1-year SVG frame counts were not significantly different between the groups based on ANCOVA (P=0.529) (Figure 6).

The diameters of the left ITA and SVG were compared on postoperative and 1-year CAG (Figure 7). The left ITA diameter significantly increased over 1 year; 2.8±0.5 (postoperative) *vs* 3.2±0.6 mm (P<0.001). The diameter of the SVG significantly decreased over 1 year: 4.4±0.8 *vs* 3.0±1.4 mm (P<0.001). On postoperative CAG, the diameter of the SVG was larger in the ULV group, but it did not reach statistical significance. The change in SVG diameter at 1 year showed a significant decrease in SVG diameter in both groups. To adjust for postoperative values, ANCOVA was performed. Comparison of SVG diameter on 1-year CAG using ANCOVA showed no significant difference in 1-year SVG diameter between the groups (P=0.210). A typical example of an SVG diameter change is shown in Figure 8.

There were two patients whose SVG was occluded: 1 in each group (P>0.999). Considering the number of anastomoses with SVGs, there were initially 68 anastomoses with SVGs in the total study patients. Among them, 61 anastomoses were evaluated on 1-year CAG, and four anastomoses were found to be occluded: 2 of 30 (6.7%) in the ULV group and 2 of 31 (6.5%) in the LLV group (P>0.999).

On postoperative CAG, 3 patients showed bidirectional competition with SVGs: 1 in the ULV group and 2 in the LLV group; but on 1-year CAG, bidirectional competition with the SVG was shown in 6 patients: 2 and 4 in the ULV and LLV groups, respectively. However, no statistical significance was found with bidirectional competition or graft occlusion. One patient needed target vessel revascularization with a percutaneous coronary intervention due to progression of native coronary artery disease. No patients died during follow-up.

4. Discussion

Even in this era of second and third generation drug-eluting stents, CABG still appears to have overt superiority in patients with triple-vessel or left main coronary artery disease, and it remains the standard of care for these patients (45). Surgeons have sought the best conduit vessels that would yield the best patient outcomes. Currently, the in situ ITA anastomosed to the left anterior descending artery territory is unquestionably essential in the absence of absolute contraindications, and CABG with all arterial conduits (especially bilateral ITAs) is believed to be the best strategy in terms of long-term survival and freedom from major adverse cardiovascular events (19).

However, the use of bilateral ITAs is not as widespread as we might expect in the real world. As described in the introduction, the incidence of the use of second arterial conduits was less than 10% in STS database and approximately 20-30% in Asia or Australia. There are several reasons for the reluctance to use second arterial conduits. First, harvesting the ITA, especially with skeletonization, requires more time to learn, and it takes longer for average surgeons to harvest the ITA than an SVG. Additionally, bilateral ITAs should be harvested sequentially. In contrast, the left ITA and

SVG could be harvested simultaneously, reducing the total operation time. Moreover, the risk of deep sternal wound infection, which develops more frequently in diabetic patients, is known to increase with bilateral ITA use (46-48). Harvesting of SVGs is technically easy, and it is easier to obtain a sufficient length. Additionally, using an SVG is more convenient then using the ITA when used as a composite graft.

Traditionally, SVGs have been used for aorto-coronary bypass, and their long-term patency has been less than that of arterial grafts. There exist a number of hypotheses for the worse long-term patency of SVGs in CABG, but it is currently believed that intimal hyperplasia and the atherosclerotic changes that occur during adaption to the high pressure of the arterial system contribute the most (49). A recent report suggested that poor target artery quality, a longer duration of surgery, the use of endoscopic vein harvesting, the use of clopidogrel or ticlopidine, and cerebrovascular disease were associated with vein graft failure, but their conclusion did not provide us with any ideas for the improvement of SVG patency (50, 51). Despite the consensus that SVG has worse long-term patency, research to improve the outcomes with SVGs has continued because of its convenience in use.

Various methods have been suggested for improving the outcomes with

SVGs. During harvesting, thermal or mechanical stress is strictly avoided (No-Touch technique) (52). Conventional pressure (>250 mm Hg) dilatation of SVGs is not applied either (36, 53). With these modifications in harvesting techniques, we have reported approximately comparable outcomes with SVGs and ITAs as second limb conduits (28, 37). Additionally, perivascular tissue can be harvested together with SVGs to preserve the vasa vasorum (54). Dr. Souza, who supports a 'No-Touch SVG harvesting' strongly, published a randomized comparison of 'No-Touch' SVG harvesting versus conventional harvesting, presenting more than 10 years of follow-up data (55).

In the real world, many surgeons have their own preferences for SVG harvesting sites. Some surgeons prefer the ULV because it has a larger diameter, and it is easier to handle. Other surgeons use the LLV because its diameter is similar to that of the ITA, and harvesting the LLV requires only superficial soft tissue dissection. However, when we examine the drawbacks, the ULV is usually much large than the ITA, which might not be beneficial for single-source Y-strategies using the ITA and SVG. Moreover, harvesting the ULV requires deep soft tissue dissection and is potentially related to harvest site wound problems. The smaller diameter of the LLV is related to more difficult handling, and the smaller diameter might limit blood flow and

lead to early thrombosis. Nevertheless, there appears to be no concrete evidence for harvest site preference.

In this study, we investigated whether SVG harvesting site influenced the outcomes of SVG remodeling and patency. There have been few studies addressing this issue. Based on the hypothesis that higher vascular compliance is related to higher future patency, Stooker and colleagues compared the pressure compliance of SVGs from the upper or lower legs, but no harvest site preference could be concluded from the study (42). McLean and colleagues suggested that small target vessel diameter, female sex, and low mean graft blood flow were significant risk factors for SVG thrombosis within six months (21). However, to our knowledge, there appeared to be no immuno-histochemical or patency comparisons related to harvest site.

The remodeling of SVGs used for CABG has been studied, but the mechanism and direction of remodeling require further research (56-59). Even the definitions of ‘positive’ or ‘negative’ remodeling have been different among studies. However, ‘positive remodeling’ and ‘negative remodeling’ generally indicate ‘increased luminal diameter’ and ‘decreased luminal diameter’, respectively, and the same definitions were used in this

report. Both positive and negative remodeling can occur during the first year after CABG, and no predictors of positive or negative remodeling have been found. Because the diameter of the upper leg vein is larger than that of lower leg vein on average, we believed that the SVGs could behave differently based on harvest site. Additionally, we were interested in graft blood flow because blood stasis was related to hypercoagulability. Our initial hypotheses were that SVGs from the lower legs could show positive remodeling more frequently, and blood flow in the lower leg vein would be more rapid shown on 1-year CAG.

This study had several key findings. First, the diameters of the SVGs increased, and intimal thickness decreased significantly after exposure to arterial pressure. The second finding was that there were no significant differences in the degree of endothelial integrity, expression of VSMC activation-related proteins or smooth muscle folding between upper and lower leg veins. The third finding was that the diameter of the SVG generally decreased during the first year after CABG, but there was no significant difference in SVG diameter on 1-year CAG between the groups. Additionally, the blood flow velocity in the SVGs generally increased (SVG filling frame count decreased) during the first year, regardless of the harvest site.

The intimal thinning, lower degree of endothelial integrity and loss of medial smooth muscle folding after exposure to arterial pressure were consistent with our previous study (36). However, the difference related to harvest site was unclear in our data. In fact, the profound destruction of endothelial structures after exposure to arterial pressure prevented more reliable histopathologic evaluations. This structural damage was shown in both groups with varying severity.

Although harvesting the SVG from the upper leg requires substantial deep soft tissue dissection, using the upper leg vein was not clearly associated with maintaining the Jackson Pratt drain longer in the harvest site wound. However, a significant difference could have been found had the sample size been sufficiently larger.

In terms of remodeling, the SVGs showed negative remodeling in both groups (Figure 8), and there was no relationship with harvest site. The increased blood flow velocity in the SVGs was similar in the upper and lower leg vein groups. The incidence of SVG anastomosis site occlusion at 1 year was also similar in both groups. The patency of SVGs at 1 year could be more significantly related to target vessel status and not to the SVG flow velocity or luminal diameter. The diameter change in SVG was relatively

consistent over the whole SVG length.

Although we began our study with the assumption that upper leg veins are generally bigger than lower leg veins, there were substantial size overlaps between the groups. Some veins from lower legs were frequently larger than upper leg veins in diameter. Considering not the harvest site but the SVG diameter itself could be more significant for graft characteristics and future remodeling. Had we grouped the patients based on SVG diameter, the results could have been different. However, determining the proper harvest site depending on strictly measured SVG diameter is infeasible in clinical practice. We often determine 'where to harvest' in the operating room based on visual inspection of the leg vein route and size.

This study had limitations. First, the study subject number was relatively small. Although sample size was calculated using statistical methods, ethical considerations about obtaining human tissue specimens played a major role in determining study sample size. Consequently, multivariable analyses to determine the effects of other variables were impossible. Second, histopathologic analyses were performed only on intraoperatively obtained vessel specimens. For the evaluation at 1 year, virtual histology using intravascular ultrasound or optical coherence tomography might have been

better to determine the changes in SVG wall structure (60-62).

5. References

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Table 1. Inclusion and exclusion criteria. CABG, coronary artery bypass grafting; EF, ejection fraction

Inclusion criteria
Patients requiring CABG due to multivessel coronary artery disease (40-75 years old)
Off-pump CABG
Primary graft is in situ left internal thoracic artery.
Second limb conduit is required for lateral and inferior wall revascularization
No limitation in harvest sites for saphenous vein grafts
Informed consent from the patient and family
Exclusion criteria
Severe left ventricular dysfunction (EF <25%)
Cardiomegaly defined as cardiothoracic ratio > 0.7
Current evidence of malignancy
No evidence of cure from cancer
Ongoing infection
On pump conversion during CABG
Concomitant valve surgery or ventricular restoration surgery
Critical comorbidities with expected lifespan < 1 year

Table 2. Baseline patient characteristics. CRF, chronic renal failure; RWMA, regional wall motion abnormality.

	Upper leg group (n=13)	**Lower leg group (n=13)**	***P* value**	**Total (n=26)**
Male	10 (77%)	10 (77%)	>0.999	20 (77%)
Age (years)	66±7	63±7	0.486	65±7
Smoker	3 (23%)	6 (46%)	0.411	9 (35%)
Hypertension	9 (69%)	5 (38%)	0.238	14 (54%)
Diabetes	5 (38%)	8 (62%)	0.434	13 (50%)
Dyslipidemia	1 (8%)	5 (38%)	0.160	6 (23%)
Stroke history	2 (15%)	1 (8%)	>0.999	3 (12%)
CRF	2 (15%)	2 (15%)	>0.999	3 (12%)
Left main disease	5 (38%)	10 (77%)	0.111	15 (58%)
RWMA	3 (23%)	7 (54%)	0.226	10 (38%)
Diagnosis			0.265	
Unstable angina	7 (54%)	4 (31%)		11 (42%)
Stable angina	6 (46%)	7 (54%)		13 (50%)
Postinfarct angina	0 (0%)	2 (15%)		2 (8%)
Emergency operation	0 (0%)	1 (1%)	>0.999	1 (4%)

Table 3. Operative data. SVG, saphenous vein graft; TTFM, transit time flow measurement; RCA, right coronary artery.

	Upper leg group (n=13)	**Lower leg group (n=13)**	***P* value**	**Total (n=26)**
Number of total revascularization	3.6±0.8	3.6±0.7	0.938	3.6±0.7
Number of revascularization (SVG)	2.6±0.8	2.6±0.7	0.938	2.6±0.7
SVG flow (mL/min) measured with TTFM	31±22	29±18	0.890	30±20
SVG to Y flow ratio	0.6±0.2	0.5±0.2	0.129	0.6±0.2
Length of harvested SVG (cm)	22±2.0	22±1.9	0.869	22±1.9
Length of residual SVG after all anastomosis (cm)	4.5±1.8	4.5±1.6	0.829	4.5±1.6
Harvest site				
Left leg	10 (77%)	12 (92%)	-	-
Right leg	3 (23%)	1 (8%)	-	-
Target vessel				
Left anterior descending	13 (100%)	10 (77%)	0.220	23 (89%)
Diagonal	8 (62%)	9 (69%)	>0.999	17 (65%)
Ramus intermedius	1 (8%)	3 (23%)	0.593	4 (15%)
Obtuse marginal	12 (92%)	12 (92%)	>0.999	24 (92%)
Distal RCA	1 (8%)	0 (0%)	>0.999	1 (4%)
Posterior descending artery	7 (54%)	8 (62%)	>0.999	15 (58%)
Posterolateral branch	4 (31%)	3 (23%)	>0.999	7 (27%)

Table 4. Microscopic measurement of luminal diameter, intimal and medial thickness. *P* values for comparison are presented in Figure 5.

Diameter or thickness (micrometer)	**Upper leg vein**			**Lower leg vein**		
	Distal	Proximal	Dilated	Distal	Proximal	Dilated
Lumen	673±181	858±266	1477±353	631±184	623±143	1138±419
Intima	175±72	218±114	132±124	136±45	175±61	67±52
Media	268±85	275±88	259±92	306±59	292±60	249±68

Table 5. Degree of endothelial integrity (H&E), expression of vascular smooth muscle cell activation related proteins (KLF4 and SRF), and preservation of media smooth muscle folding (myocardin). *Wilcoxon signed rank test.

	Upper leg group (n=13)	**Lower leg group (n=13)**	***P* value**
Hematoxylin & Eosin (H&E)			
Proximal	0.78±0.15	0.76±0.13	>0.999
Dilated	0.34±0.16	0.36±0.23	0.967
Intra-group pairwise comparison	*P<0.001	*P<0.001	
Kruppel-like factor (KLF) -4			
Proximal	0.66±0.15	0.75±0.13	0.155
Dilated	0.25±0.11	0.30±0.21	0.843
Intra-group pairwise comparison	*P<0.001	*P<0.001	
Serum response factor (SRF)			
Proximal	0.63±0.18	0.72±0.17	0.354
Dilated	0.24±0.14	0.31±0.14	0.169
Intra-group pairwise comparison	*P<0.001	*P<0.001	
Myocardin			
Proximal	0.80±0.13	0.78±0.21	>0.999
Dilated	0.22±0.09	0.29±0.16	0.238
Intra-group pairwise comparison	*P<0.001	*P<0.001	

Table 6. Change of saphenous vein graft (SVG) filling frame numbers and graft diameter in 1-year coronary angiography (CAG). Comparison between upper and lower leg vein is presented in Figure 7. *Wilcoxon signed rank test for pairwise comparison. LITA, left internal thoracic artery; Postop, postoperative; CAG, coronary angiography; SVG, saphenous vein graft.

	LITA		**Upper leg vein**		**Lower leg vein**	
	Postop. CAG	1-year CAG	Postop. CAG	1-year CAG	Postop. CAG	1-year CAG
SVG filling frames	-	-	32±12	22±12	29±12	24±8
***P* value**			0.007		0.080	
Diameter (mm)	2.8±0.5	3.2±0.6	4.6±0.8	3.5±1.6	4.1±0.8	2.5±1.1
***P* value**	<0.001		0.012		0.001	

Figure 1. Y-anastomosed in situ left internal thoracic artery and saphenous vein graft. Saphenous vein graft was harvested including perivascular tissue, with No-Touch technique (minimal manipulation).

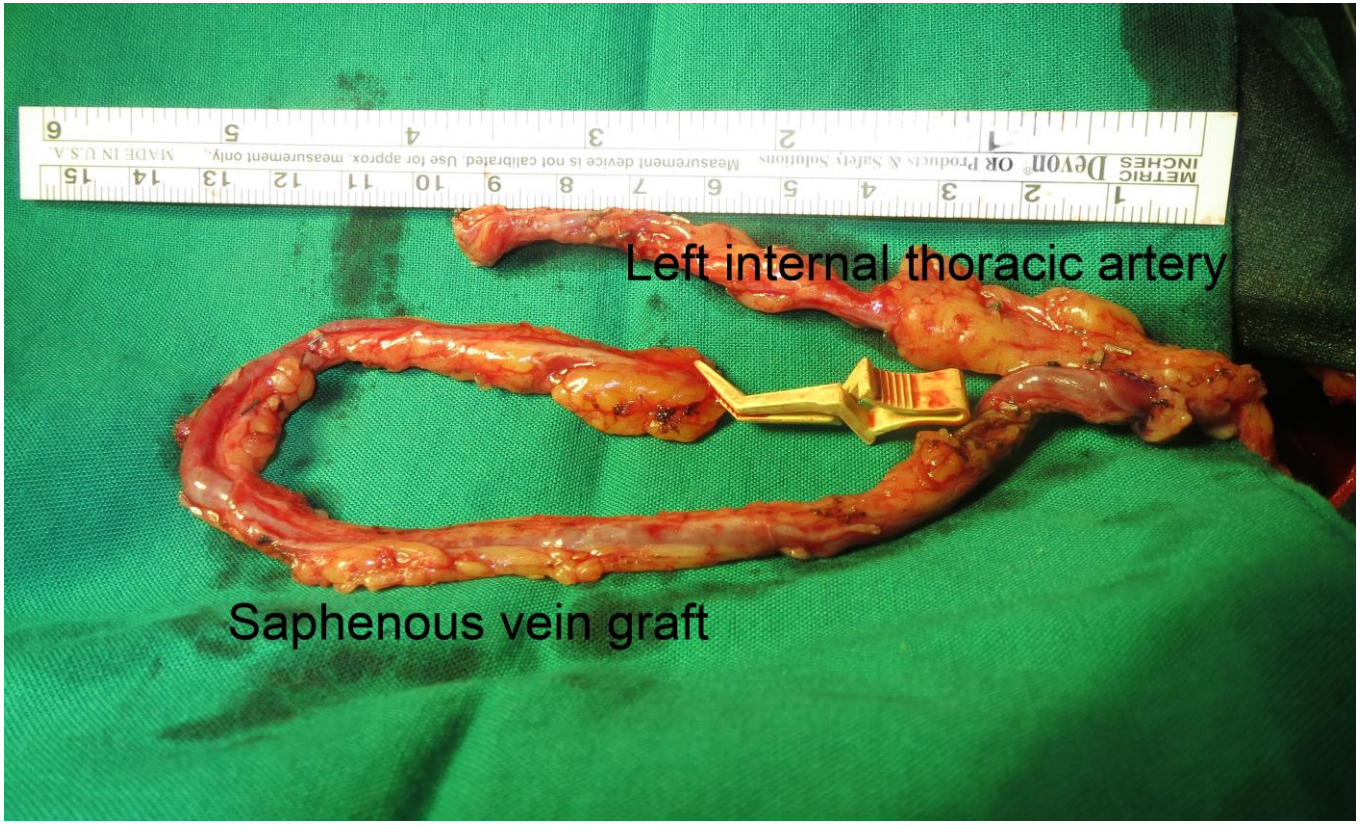
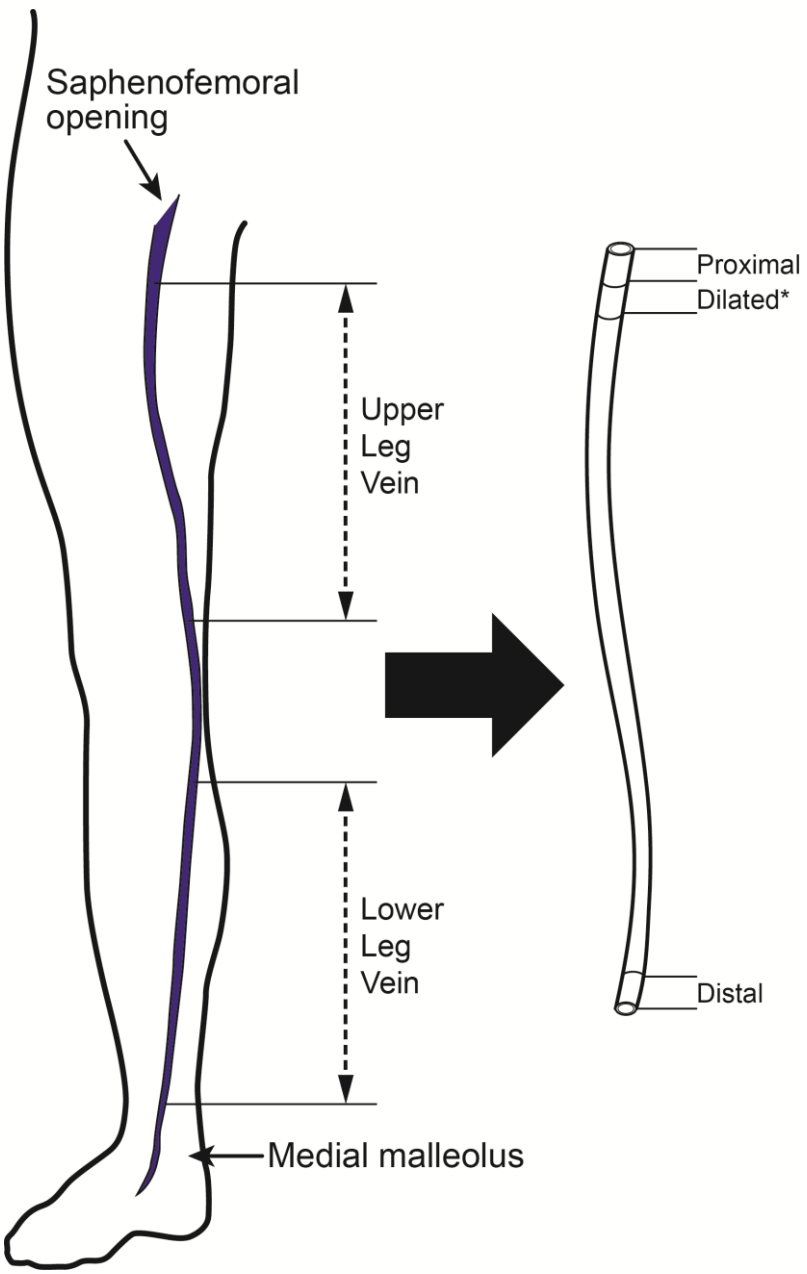


Figure 2. Schematic figure of saphenous vein harvest site randomization and tissue sampling. *Dilated sample was obtained just before last anastomosis in order to expose the vessel to native internal thoracic artery pressure.



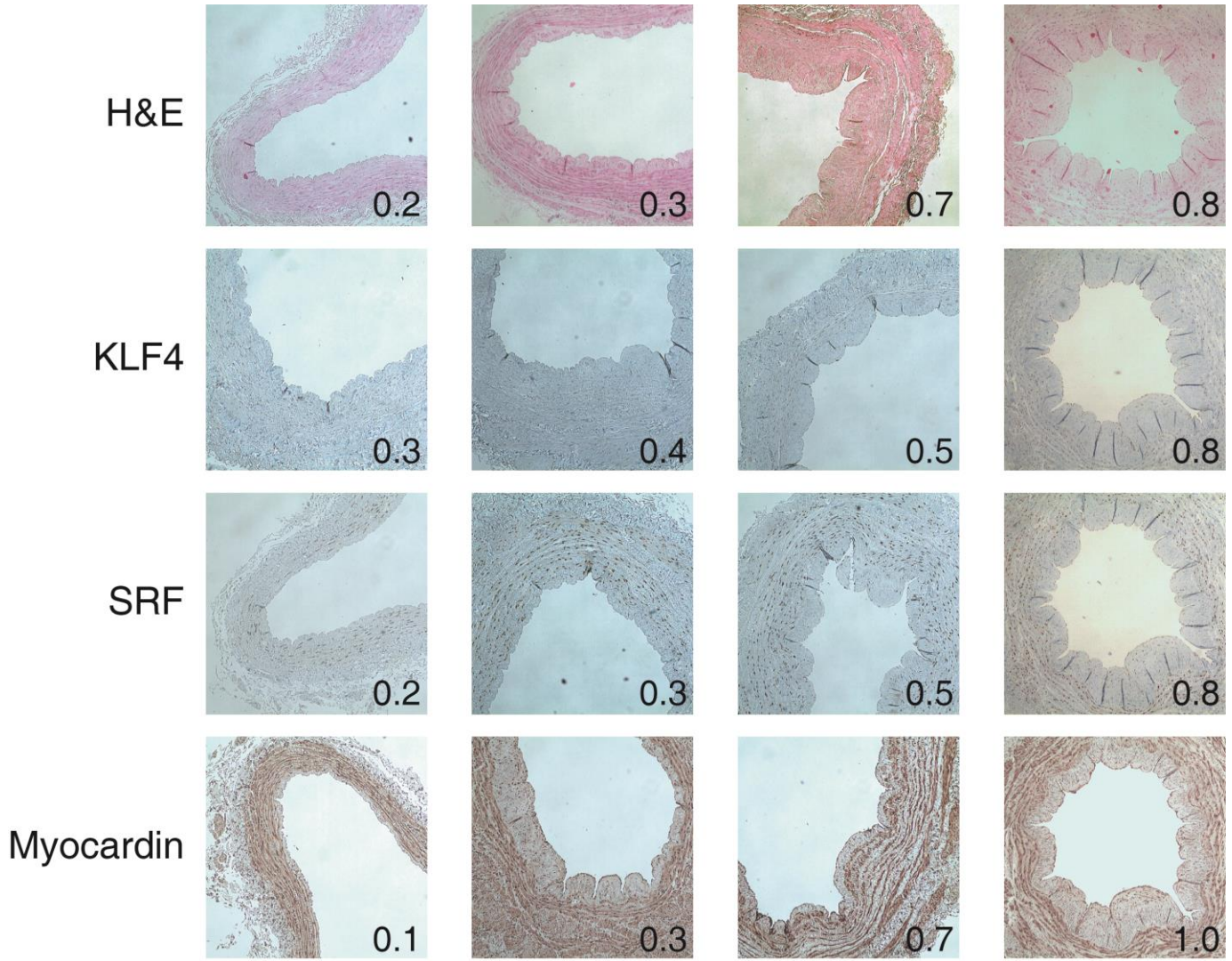


Figure 3. Typical examples of specimen; endothelial integrity (H&E), expression of vascular smooth muscle cell (VSMC) activation related proteins (KLF4 and SRF), and preservation of smooth muscle folding (myocardin). Numbers indicate degree of measured variables calculated by the proportion of positive staining in luminal circumference (between 0 and 1). H&E, hematoxylin-eosin; KLF4, Kruppel-like factor 4; SRF, serum response factor.

Figure 4. Measurement of lumen diameter, intimal and medial thickness.

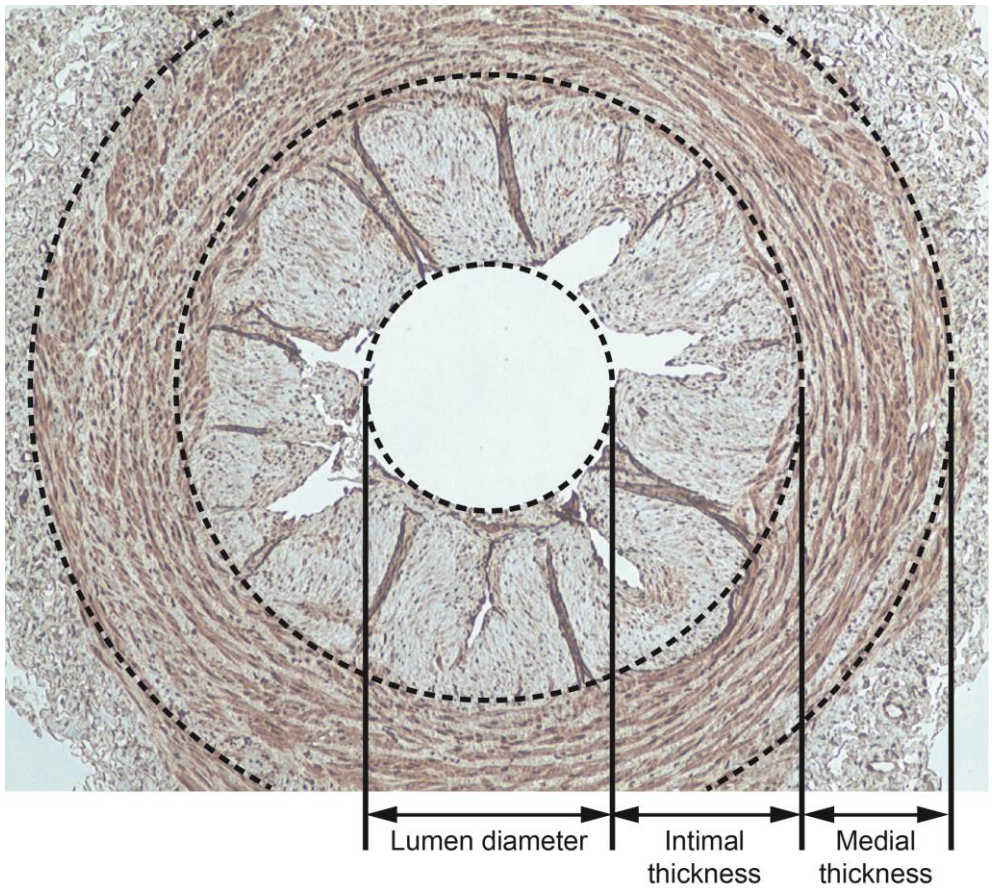
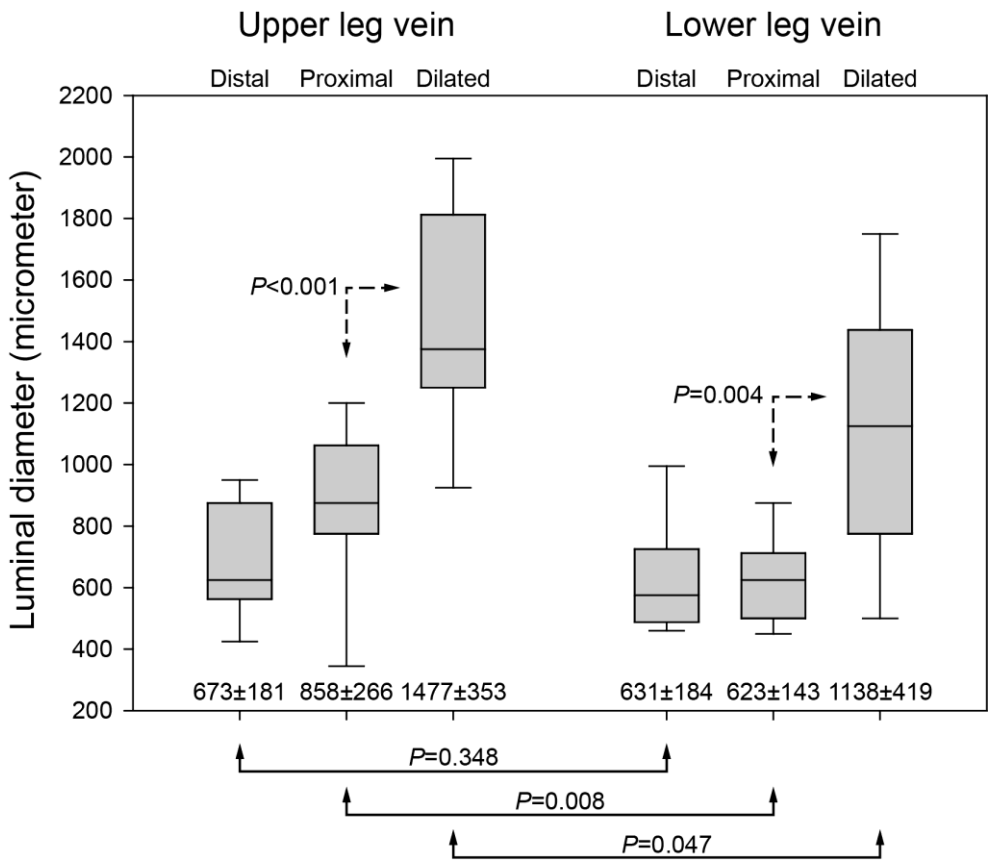
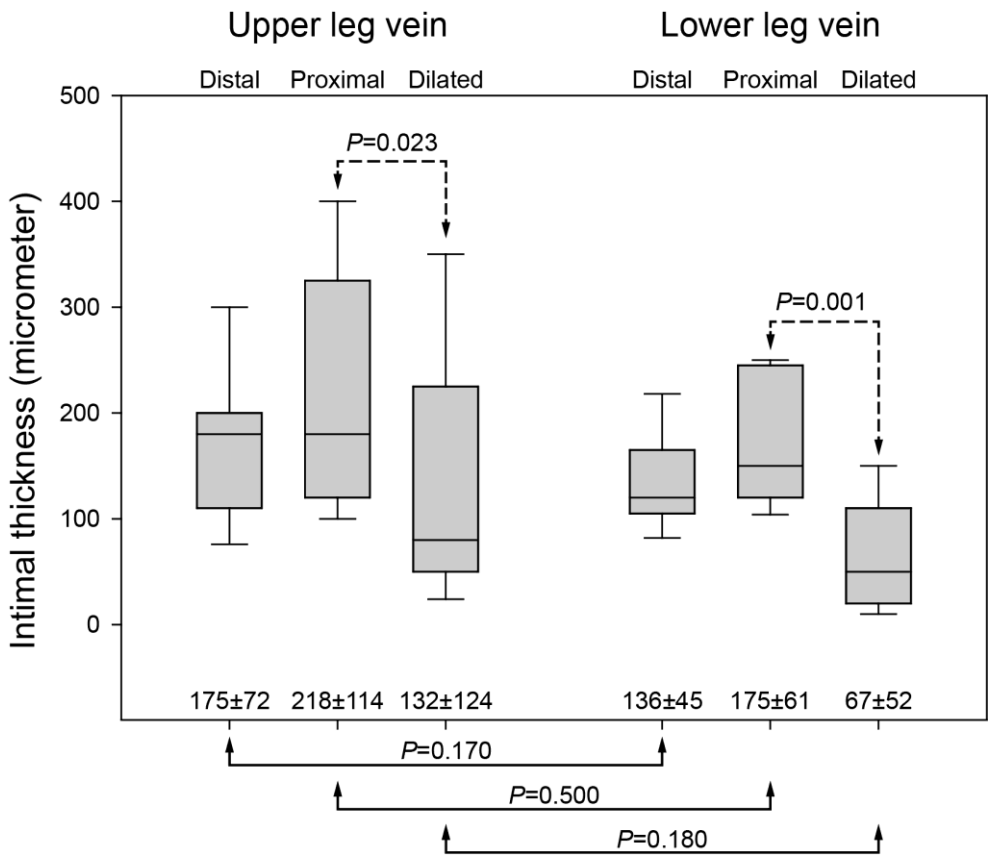


Figure 5. Luminal diameter (A), intimal (B) and medial (C) thickness in histopathologic examination.

(A)



(B)


Upper leg vein
Lower leg vein
Distal
Proximal
Dilated
Distal
Proximal
Dilated
Intimal thickness (micrometer)
500
400
300
200
100
0
P=0.023
P=0.001
175±72
218±114
132±124
136±45
175±61
67±52
P=0.170
P=0.500
P=0.180

(C)

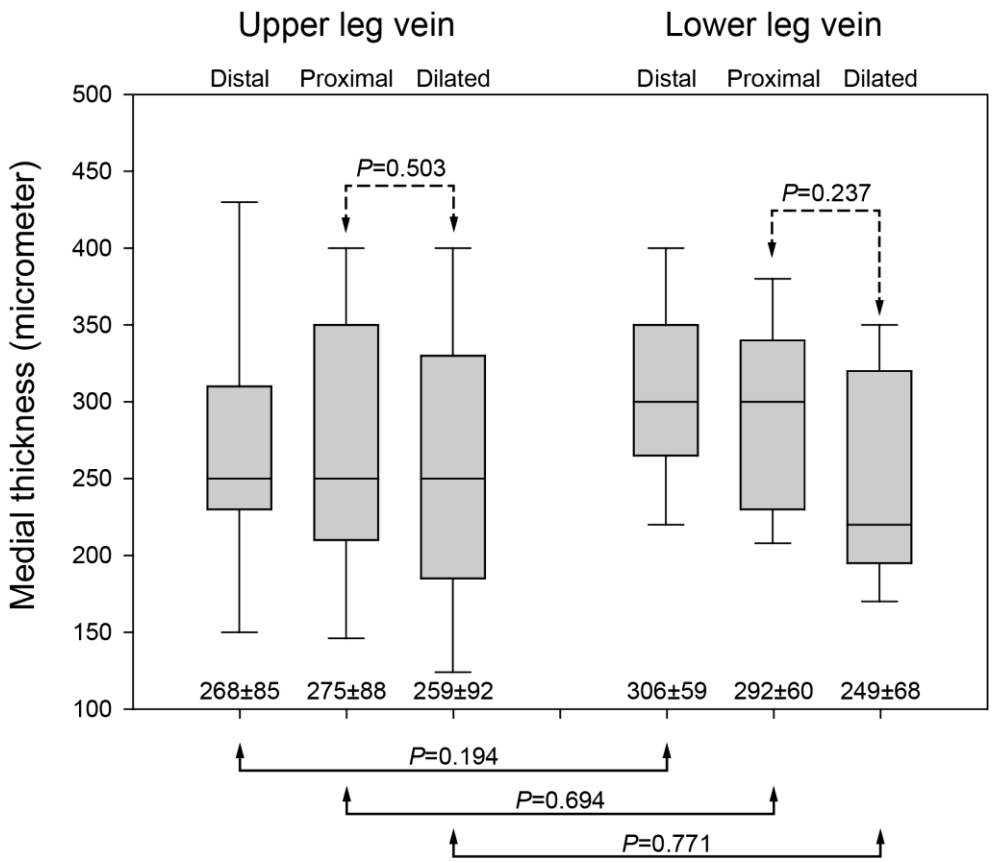

Upper leg vein
Lower leg vein
Distal
Proximal
Dilated
Distal
Proximal
Dilated
Medial thickness (micrometer)
500
450
400
350
300
250
200
150
100
P=0.503
P=0.237
268±85
275±88
259±92
306±59
292±60
249±68
P=0.194
P=0.694
P=0.771

Figure 6. Change of saphenous vein graft (SVG) filling frame numbers in upper and lower leg vein group. *P value from ANCOVA (analysis of covariance), adjusting postoperative values.

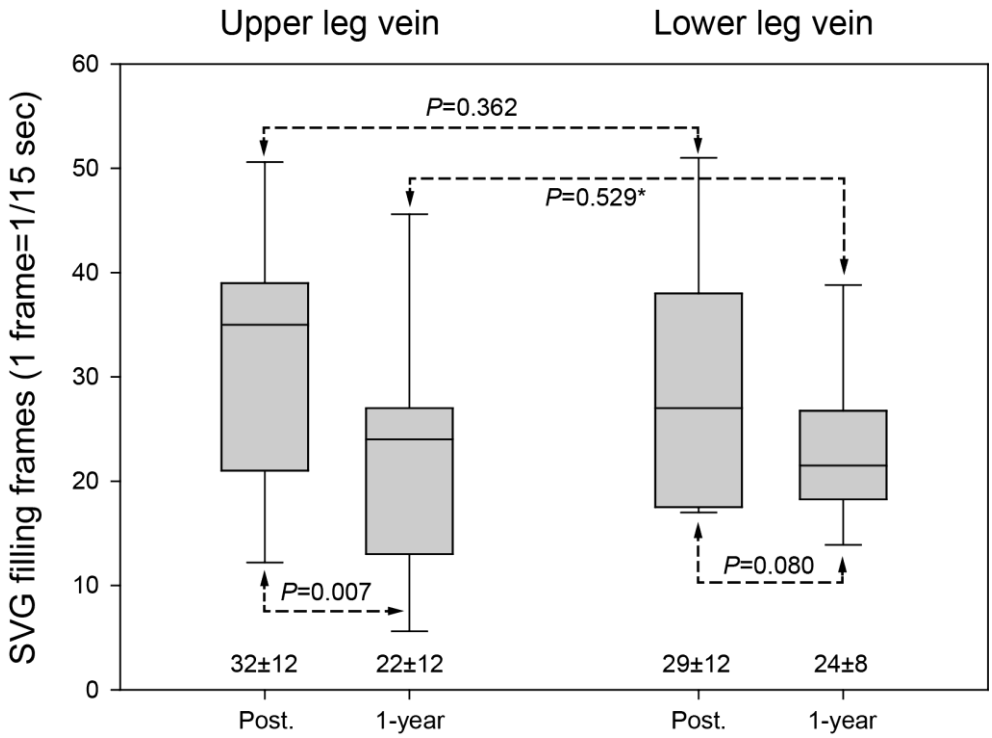


Figure 7. Change of graft diameter in angiography. *P value from ANCOVA (analysis of covariance), adjusting postoperative vein diameter. LITA, left internal thoracic artery.

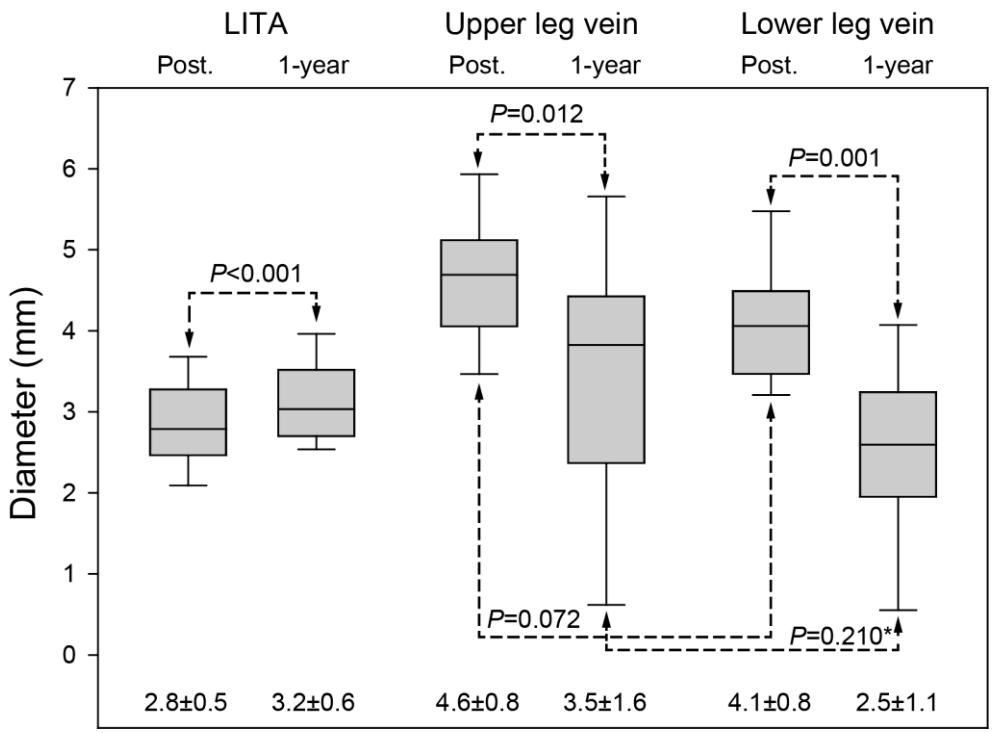
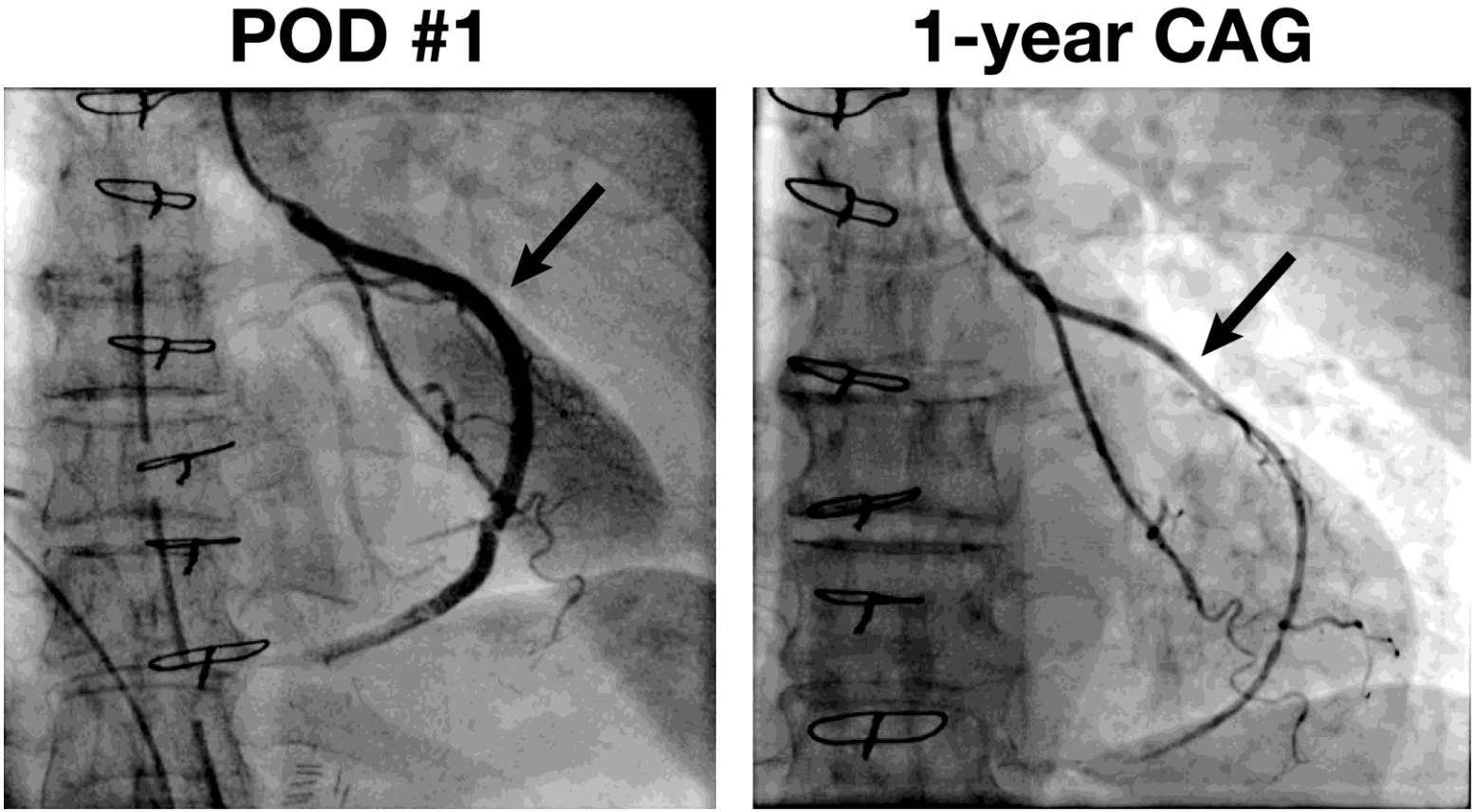


Figure 8. A typical example of SVG diameter change is shown in postoperative and 1-year coronary angiography (CAG). Arrow indicates saphenous vein graft. POD, postoperative day.



국문 초록

관상동맥우회술(冠狀動脈迂廻術)에서 동맥 도관(導管)만을 사용하는 것이 가장 좋은 장기 성적(長期 成績)을 가진다는 점은 이미 주지(周知)의 사실이나, 실제로 제 2 도관으로는 복재정맥(伏在靜脈)이 가장 빈번하게 사용되고 있다. 그 주된 이유는 복재정맥이 채취(採取)하기에 편리하고 쉽게 충분한 길이로 획득(獲得)할 수 있기 때문이다. 본 연구에서는, 관상동맥우회술에 사용하는 복재정맥 도관(伏在靜脈 導管)의 성적을 개선(改善)하고자 하는 노력의 일환(一環)으로, 복재정맥 도관을 허벅지부위와 종아리부위에서 채취한 것으로 나누어 서로 비교하고자 하였으며, 그 방법으로 면역조직화학(免疫組織化學) 분석과 1 년 추적(追跡) 심혈관 조영술(心血管 造影術)을 시행하였다.

다중(多重) 관상동맥질환으로 인공심폐기(人工心肺機)의 보조(補助) 없는 관상동맥우회술을 시행받는 40-75 세 환자를 대상으로 하였다. 총 26 명의 환자를 허벅지정맥 군(群)과 종아리정맥 군으로 각 13 명씩 무작위(無作爲) 배정하였다. 모든 복재정맥은 '노터치' 방법을 이용하여 채취하였으며, 이 때 정맥 주위의 조직을 포함하여 채취하였다. 정맥에 압력을 가하여 확장하는 기법은 사용하지 않았다. 복재정맥을 좌측 내흉동맥(內胸動脈)에 Y 형태로 문합(吻合)하기 전에, 복재정맥의 원위부(遠位部, distal) 및 근위부(近位部,

proximal) 말단(末端)을 샘플링하였다. 또한, 복재정맥을 내흉동맥에 Y 형태로 문합한 뒤에, 내흉동맥의 압력에 의해 수동적(受動的)으로 부풀려진 복재정맥의 말단(확장후(擴張後), dilated)를 최종 관상동맥 문합 직전에 샘플링하였다. 이 샘플들을 병리조직학적(病理組織學的)으로 분석하였다. 헤마톡실린-에오신(H&E) 염색, 크루펠 유사요소(KLF)-4, 혈장 반응요소(SRF), 마이오카딘(myocardin) 염색을 시행하였다. 혈관 내피(內皮)의 온전성(穩全性), 혈관 평활근(平滑筋) 세포 활성화(細胞 活性化)에 연관(聯關)된 단백질들의 발현(發現), 혈관 중간막(中間膜)에 있는 평활근의 주름, 내경(內徑), 내막(內膜)과 중간막의 두께를 측정하였다. 수술 직후(直後)와 1 년째에 심혈관 조영술을 시행하였다. 심혈관 조영술 결과로부터 복재정맥의 직경(直徑)과 복재정맥도관을 조영제(造影劑)가 채우는 동안의 비디오 프레임수를 측정하여 혈관의 리모델링을 평가하였다.

혈관내피의 온전성, 혈관 평활근 세포 활성화에 연관된 단백질들의 발현, 혈관 중간막에 있는 평활근의 주름에 대하여 복재정맥의 채취 부위에 따른 유의미(有意味)한 차이는 없었다. 원래 '근위부' 샘플의 바로 옆에서 채취한 것에 해당하는 '확장후' 샘플은 두 군 모두에서 유의(有意)하게 더 큰 내경을 보였다; 허벅지 군에서 '확장후' 1477±353 μm 對 '근위부' 858±266 μm, P<0.001, 종아리 군에서 '확장후' 1138±419 μm 對 '근위부' 623±143 μm, P=0.003. 또한, '확장후' 샘플은 '근위부' 샘플에 비해 내막이 훨씬 얇았다; 허벅지 군에서 '확장후' 132±124 μm 對 '근위부' 218±114 μm,

P=0.036, 종아리 군에서 '확장후' 67±52 μm 對 '근위부' 175±61 μm, *P*<0.001. 그러나, 허벅지 군과 종아리 군의 상호 비교에서는 유의미한 차이가 없었다. 전체 환자 중 24 명(92%)에서 1 년 추적 심혈관 조영술을 시행하였다. 그 결과, 평균적으로 복재정맥 도관은 수술 후 1 년 동안 그 직경이 감소하는 것으로 나타났다; 허벅지 군에서 수술 직후 4.6±0.8 mm 對 1 년째 3.5±1.6 mm, *P*=0.012, 종아리 군에서 수술 직후 4.1±0.8 mm 對 1 년째 2.5±1.1 mm, *P*=0.001). 그러나, 복재정맥 직경의 감소를 허벅지 군과 종아리 군 간에 서로 비교했을 때에는 유의미한 차이가 없었다. (공분산분석(共分散分析), *P*=0.210). 1 년째 심혈관조영술에서 2 명(8%)의 환자가 우회도관(迂廻導管) 막힘을 보였다; 허벅지 군에서 1 명(8%), 종아리 군에서 1 명(8%), *P*>0.999. 복재정맥 도관을 조영제가 채우는 동안의 비디오 프레임 수는 수술 후 1 년동안 두 군에서 공통적으로 감소하였지만, 마찬가지로 두 군의 상호(相互) 비교에서는 유의미한 차이가 없었다 (공분산분석, *P*=0.529).

복재정맥의 채취 부위에 따른 어떠한 뚜렷한 우월성(優越性)도 발견할 수 없었다. 허벅지에서 뗀 복재정맥과 종아리에서 뗀 복재정맥은 병리 조직학적으로 유사(類似)하였고, 수술 후 1 년동안 심혈관 조영술 검사에서의 변화도 유사하였다. 관상동맥우회술에서 제 2 도관으로 사용하는 복재정맥의 장기 변화를 평가하기 위한 추가 연구가 필요하다고 하겠다.

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