

## ORIGINAL ARTICLE

# Autologous pericardium may be an alternative carotid patch material in patient with undergoing simultaneous carotid endarterectomy and coronary artery bypass grafting

## Eş zamanlı karotis endarterektomi ve koroner arter baypas greffleme operasyonu yapılan hastalarda otolog perikard alternatif bir karotis yama materyali olabilir.

<sup>1</sup>Veysel Başar , <sup>2</sup>Emre Kubat , <sup>3</sup>Ferit Çiçekçioğlu , <sup>1</sup>Mehmed Yanartaş , <sup>1</sup>Hasan Sunar 

<sup>1</sup>Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital, Department of Cardiovascular Surgery, Istanbul, Turkey. <sup>2</sup>Gülhane Training and Research Hospital, Department of Cardiovascular Surgery, Ankara, Turkey. <sup>3</sup>Bozok University, Faculty of Medicine, Department of Cardiovascular Surgery, Yozgat, Turkey.

## Correspondence

Veysel Başar, Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kalp ve Damar Cerrahisi Kliniği

E-Mail: drveyselkv@hotmail.com

## How to cite ?

Başar V. , Kubat E. , Cicekcioglu F. , Yanartaş M. , Sunar H. Autologous pericardium may be an alternative carotid patch material in patient with undergoing simultaneous carotid endarterectomy and coronary artery bypass grafting. Genel Tıp Dergisi. 2022; 32(5): 554-558

## ABSTRACT

**Background:** Dacron, polytetrafluoroethylene, great saphenous vein, and bovine pericardium are the commonly used as patch materials. However, there is no comparative study about autologous pericardial as a patch material in carotid endarterectomy surgery. We aimed to assess the results of the use of autologous pericardial patch in patients undergoing concomitant carotid endarterectomy and coronary artery by-pass graft surgery.

**Materials and Methods:** The study involved 30 patients who underwent concomitant carotid endarterectomy with patch angioplasty and coronary artery bypass grafting surgery from January 2016 to February 2020. Patchplasty is performed with autologous pericardium for 13 patients and dacron patch for 17 patients during carotid endarterectomy.

**Results:** No statistical difference was found between the groups in terms of reoperation, arterial occlusion, restenosis, operation time, and neurological events. In the postoperative follow-up, it was determined that the amount of drainage from the area on which the carotid surgery was applied was less in the those in whom autologous pericardium was used compared to those in whom Dacron patch was used. (p=0.001)

**Conclusion:** We concluded that the use of autologous pericardium as a carotid artery patch is a safe, feasible, and effective method in patients undergoing combined carotid artery and coronary bypass surgery.

**Keywords:** Pericardium, carotid stenosis, endarterectomy, dacron, coronary artery bypass grafting

## ÖZ

**Amaç:** Dakron, politetrafloroetilen, büyük safen damarı ve sığır perikardı yaygın olarak yama malzemeleri olarak kullanılır. Ancak karotis endarterektomi cerrahisinde yama materyali olarak otolog perikardiyal ile ilgili karşılaştırılmalı bir çalışma bulunmamaktadır. Bu çalışmada, eş zamanlı karotis endarterektomi ve koroner arter baypas greft cerrahisi uygulanan hastalarda otolog perikardiyal yama kullanımının sonuçlarını değerlendirmeyi amaçladık.

**Gereç ve Yöntem:** Çalışmaya Ocak 2016 ile Şubat 2020 arasında yama anjiyoplasti ve koroner arter baypas greffleme cerrahisi ile birlikte karotis endarterektomi uygulanan 30 hasta dahil edildi. Karotis endarterektomi sırasında 13 hastada otolog perikard ve 17 hastada dakron yama ile patchplasti yapıldı.

**Bulgular:** Gruplar arasında reoperasyon, oklüzyon, restenoz, operasyon süresi ve nörolojik olaylar açısından istatistiksel fark bulunmadı. Postoperatif takipte otolog perikard kullanılanlarda karotis cerrahisi uygulanan bölgeden drenaj miktarının Dacron yama uygulananlara göre daha az olduğu belirlendi. (p=0,001)

**Sonuç:** Karotis arter yaması olarak otolog perikardın kullanımının karotid arter ve koroner bypass cerrahisi uygulanan hastalarda güvenli, uygulanabilir ve etkili bir yöntem olduğu sonucuna vardık.

**Anahtar Kelimeler:** Perikard, karotis darlığı, endarterektomi, dakron, koroner arter baypas greffleme

## Introduction

Stroke is a dreaded complication after coronary artery bypass grafting (CABG) due to high risk of mortality, morbidity, long hospitalization, and impaired quality of life. Although many risk factors have been defined for CABG-related stroke, some authors have considered the presence of aortic atheroma, carotid stenosis, and peripheral vascular disease as more effective factors (19). The prevalence of significant carotid artery stenosis (CAS) (>70%) in patients who are candidate for CABG varies from 3.6% to 8.8% (2,3). Although there is consensus in the guidelines on treatment management in patients in whom coronary artery disease or CAS exists alone, there are many

controversial issues in the surgical management of the patient group in which both exist at the same time. One of them, there is no consensus on the best patch material to use in such patients. Dacron, polytetrafluoroethylene, great saphenous vein, and bovine pericardium are the commonly used patch materials, and there are many studies in the literature about these patches (4). The use of autologous pericardium as an alternative carotid patch in concomitant carotid endarterectomy (CEA) and CABG surgery in four cases has been described previously (5). However, there is no comparative study between autologous pericardial patch and Dacron patch material. Therefore, in this comparative study, we

aimed to assess the results of the use of autologous pericardial patch in patients undergoing concomitant CEA and coronary artery by-pass graft surgery.

## Materials and Methods

### Patient population

This retrospective, cross-sectional comparative study involved 30 patients who underwent concomitant CEA with patch angioplasty and CABG surgery from January 2016 to February 2020. Patients who underwent CEA with primary suturing OR eversion technique and staged surgery (such as CEA after CABG) were excluded. The patients were divided into two groups according to the patch material. Thirteen patients underwent CEA and patchplasty with autologous pericardium (group 1) and 17 patients had CEA and patchplasty with Dacron (Group 2). Data such as demographics, procedures, doppler ultrasonography(DUS) results and outcomes were collected from the electronic database of the hospital and patient files. Postoperative bleeding, 30-day stroke, and mortality were the primary endpoint of the study. Carotid restenosis and thrombosis were the secondary endpoint of the study.

In patients undergoing CABG, carotid DUS was performed in symptomatic patients or asymptomatic patients with age  $\geq$  70 years, multivessel coronary artery disease, concomitant lower extremity arterial disease, or carotid bruit (6,7). Symptomatic patient was defined as having a recent (<6 months) history of stroke/TIA (6,7). Stenosis grade was determined based on the CT scan screening according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. Concomitant CEA surgery was planned according to guideline recommendation (6-8). Restenosis threshold of the carotid artery after endarterectomy was accepted as 70% (at the endarterectomy site), which was diagnosed with either conventional angiography or computed tomography (CT) angiography (7). Post-operative stroke was confirmed by an attending neurologist based on any major neurological deficit diagnosed either clinically or with a head CT scan.

The Institutional Review Board approved the study protocol (Date:09.02.2021 #2021/3/474). The study was conducted in accordance with the principles of the Declaration of Helsinki. A written informed consent was obtained from each patient for surgical procedure.

### Surgical procedure

Near-infrared spectroscopy monitoring was used routinely to assess oxygen saturation of the brain in all surgical procedures. Carotid shunt was applied selectively according to carotid stump pressure.

Group 1 consisted of patients who underwent CEA and patchplasty with autologous pericardium. Following classical incision medial to the sternocleidomastoid muscle, the common carotid, external carotid, and internal carotid arteries were explored. After midline sternotomy, at least a 2×5 cm pericardium (pericardial size may change according to stenotic segment) were

harvested. Adipose tissue over the pericardium was removed. Pericardium was attached on the plate with the rough surface facing upwards. The pericardium was soaked in 2% glutaraldehyde solution for 5 min for fixation. It was, then, rinsed with saline solution. Diaphragmatic side of the pericardium is thicker than the other side (9). Therefore, the diaphragmatic side of the pericardium was used for this procedure. After 5000 IU of heparin was administered, vascular clamps were applied. After the longitudinal arteriotomy was extended from the common carotid artery to the internal carotid artery, carotid shunt canula was inserted. The plaque inside the carotid artery was carefully separated and removed. After the removal of the plaque by de-airing maneuvers, surgical closure was performed with a pericardial patch using 6/0 polypropylene with the continuous-suturing technique. The smooth surface of the pericardium should be placed towards the lumen of the vessel. Then, the vascular clamps were removed in an appropriate order and the flow was restored. After the procedure was completed, standard on-pump CABG was performed in all patients.

Group 2 involving CEA and surgical closure with the Dacron patch was performed by the same technique as described above for Group 1. After the CEA procedure was completed, midline sternotomy was performed for on-pump CABG surgery.

### Follow-up

Following the surgery, all patients were taken to the Cardiovascular Surgery Intensive Care Unit for follow-up. Postoperative bleeding volume was recorded on a daily basis from all surgical drains until the removal of these instruments. The patients were then transferred to the cardiovascular surgery clinic when their general condition and hemodynamics were good. Dual anti-platelet therapy, consisting of 100-mg acetylsalicylic acid and 75-mg clopidogrel was routinely administered in all patients. At follow-up, the patients were evaluated with physical examination and color DUS in the outpatient clinic.

### Statistical Analysis

The data obtained in this study were analyzed using the Statistical Package for the Social Sciences version 11.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed in mean standard deviation (SD) or median(min-max), while categorical variables were expressed in number and percentage. The Student's t-test was used to analyze significant differences between normally distributed data, and the Mann-Whitney U test was used to analyze nonnormally distributed data. The chi-square and Fisher exact tests were used to examine quantitative variables. A p value of <0.05 was considered statistically significant.

### Results

A total of 30 patients who underwent concomitant CEA with patchplasty and CABG were included in this analysis. Of the patients included, 8 (26.7%) were females and 21 (73.3%) were males. The mean age of the patients was  $67.8 \pm 8.1$  years (range, 52 to 82).

The mean body mass index (BMI) was  $28.2 \pm 4.9$  kg/m<sup>2</sup> (range, 16.7 to 42.7). Hypertension (70%) was the most common comorbidity. Eight patients (26.7%) were smokers. A comparison of the groups in terms of their demographic data are presented in Table 1. There was no significant difference between groups in terms of demographics and intraoperative variables (Table 1,2).

Transient neurologic deficit was seen in three patients (10%). In the group in which autologous pericardium was used, 2/5 muscle strength loss occurred in the left upper extremity in 1 (7.7%) patient. In the group in which Dacron patch was used, neurocognitive impairment was seen in two patients (11.6%). These symptoms resolved two weeks after the surgery. Permanent neurologic deficit was not seen in both groups. Postoperative cardiac complication was seen in five patients (29.1%) in group in which Dacron patch was used. There was no statistical difference between groups in terms of sternal drainage. However, the amount of postoperative drainage from the carotid region was significantly higher in the Dacron patch group than in the autologous pericardium group ( $75.9 \pm 50.3$ ;  $27.3 \pm 23.8$ , respectively,  $p=0.001$ ). Postoperative re-exploration was performed for the carotid region in one patient due to neck hematoma in the Dacron patch group.

There were statistical differences between groups in terms of ICU and hospital stay among postoperative variables ( $p=0.01$ , both) (Table 3). There was no difference between the groups in terms of hospital and 30-day mortality due to CEA. Mean follow up was  $27.4 \pm 14.3$  months (range: 7.1-55.9). Postoperative DUS controls of the patients revealed that there were no residual stenosis, thrombosis, or aneurysm formation in both groups.

**Table 1.** Preoperative characteristics of the patients

	Perikardial Patch (n=13)	Dacron Patch (n=17)	P value
	Mean±SD	Mean±SD	
Age	66.6±8.7	68.7±7.8	0.95 <sup>a</sup>
EF	53.1±12.2	55.9±10.6	0.56 <sup>b</sup>
BMI	28±2.9	28.3±6.1	0.06 <sup>a</sup>
	n (%)	n (%)	
Gender			0.24 <sup>c</sup>
Male	5 (38.5%)	3 (17.6%)	
Female	8 (61.5%)	14 (82.4%)	
HT	10 (76.9%)	11 (64.7%)	0.691 <sup>c</sup>
DM	7 (53.8%)	7 (41.2%)	0.491 <sup>d</sup>
COPD	4 (30.8%)	7 (41.2%)	0.708 <sup>c</sup>
Smoking	5 (38.5%)	3 (17.6%)	0.242 <sup>c</sup>

EF: Ejection fraction ; BMI: Body mass index; HT: Hypertension; COPD: Chronic obstructive pulmonary disease; DM: Diabetes Mellitus; SD: Standard deviation; a: Student T test; b: Mann-Whitney U test; c: Fischer's exact test; d: Chi-square test.

**Table 2.** Intraoperative variables of the patients

	Perikardial Patch (n=13)	Dacron Patch (n=17)	P value
	Mean±SD	Mean±SD	
Duration of Operation (min)	330.8±42.3	313.2±50.1	0.48 <sup>a</sup>
Duration of XCL (min)	63.6±16.9	61.6±35.1	0.26 <sup>b</sup>
Duration of CPB (min)	111.1±24.2	107.4±37	0.32 <sup>b</sup>
	n (%)	n (%)	
Side of CEA			0.96 <sup>c</sup>
Right	6 (46.2%)	8 (47.1%)	
Left	7 (53.8%)	9 (52.9%)	
Carotid shunt usage	9 (69.2%)	9 (52.9%)	0.367 <sup>c</sup>

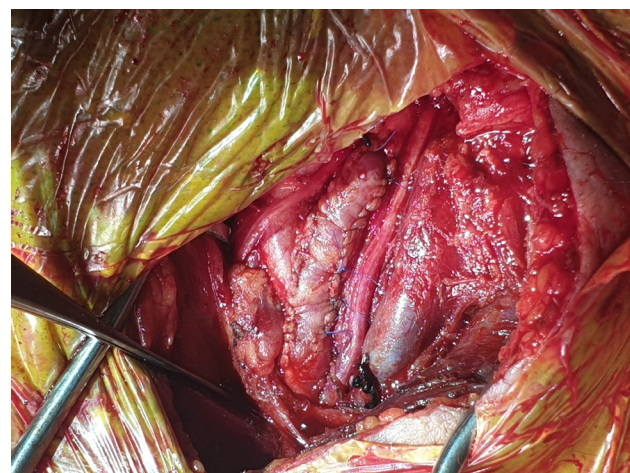
XCL: Cross clamp; CPB: Cardiopulmonary bypass; CEA: Carotid endarterectomy

SD: Standard deviation; a: Student T test; b: Mann-Whitney U test; c: Chi-square test;

**Table 3.** Postoperative outcomes of the patients

	Perikardial Patch (n=13)	Dacron Patch (n=17)	P value
	Mean±SD	Mean±SD	
Intubation period (hours)	23.8±41.1	30.3±45.7	0.17 <sup>a</sup>
Length of stay at intensive care unit (hours)	55.9±40.7	117.8±86.3	0.03 <sup>a</sup>
Length of stay at the hospital (days)	7.2±2.2	13.8±10.3	0.01 <sup>a</sup>
Drainage from the carotid region (ml)	27.3±23.8	75.9±50.3	0.001 <sup>a</sup>
Drainage from the mediastinal region (ml)	546.2±335.1		0.86 <sup>b</sup>
	n (%)	n (%)	
Cardiac complication	0 (0%)	5 (29.4%)	0.05 <sup>c</sup>
Neurologic complication	1 (7.7%)	2 (11.8%)	1 <sup>c</sup>
Re-exploration at the carotid region	0 (0%)	1 (5.9%)	1 <sup>c</sup>

SD: Standard deviation; a: Mann-Whitney U test ; b :Student T test; c: Fischer's exact test



**Figure 1.** Intraoperative image of carotid endarterectomy and patchplasty with autologous pericardium

## Discussion

Hemodynamically significant internal carotid artery stenosis, which was detected before cardiac surgery, simultaneous or staged CEA was performed. The timing and modality of the carotid revascularization is controversial, and it should be individualized based on the clinical situation, the level of emergency, and the severity of the carotid and coronary artery diseases (6,7). Staged CEA strategies cause a higher risk of periprocedural MI if the carotid artery is revascularized first, and a trend toward increased cerebral risk occurs if CABG is performed first. In a study examining different strategies that can be applied, it was found that 3-month stroke and mortality rates were higher in patients with unilateral CAS in CAE performed after CABG compared to prior CAE in concomitant CABG or staged surgery (10). It has been known that staged or simultaneous techniques have advantages and disadvantages compared to each other. In a recent meta-analysis, it was found that there was no significant difference in 1-year mortality, transient neurological deficit, or MI rates, despite longer hospital stay and less 30-day mortality and stroke in staged surgery (11). However, it should be kept in mind that when staged surgery is preferred, patients are likely to be exposed to an interstage cardiovascular event. Since our surgical center has a high patient circulation, simultaneous surgery is preferred because it requires shorter hospital stay. Therefore, simultaneous surgery was performed in all patients included in our study.

With the developments in technology, the number and variety of bio-prosthesis materials used in cardiovascular surgery are increasing. Compared to synthetic materials, pericardial patches are an inexpensive, readily available, infection-resistant, and biocompatible material (12). Autologous pericardium can be used fresh or treated with glutaraldehyde. However, autologous pericardium may be retracted when used fresh. For this reason, glutaraldehyde-fixed autologous pericardium has been used for many years in many congenital or reconstructive operations in cardiac surgery. When autologous pericardium is fixed with glutaraldehyde, it becomes tougher, stronger, more resistant to proteolytic degradation, and more convenient to surgical manipulation (13,14). However, the autologous pericardium does not have an optimal method and duration of glutaraldehyde fixation (14). However, residual unstable glutaraldehyde polymers remaining during fixation are known to cause inflammatory reaction, cytotoxicity, and calcification, in addition to inhibiting endothelialization (13). In a study, it was determined that five-minute fixation with 2% glutaraldehyde caused optimal tensile strength and elongation for the autologous pericardium (5). In our study, autologous pericardium was fixed with 2% glutaraldehyde for 5 minutes. In this way, surgical manipulation of the fixed pericardium was easy and the operation time was not prolonged. However, no inflammatory reaction, stroke, or mortality was observed associated with the use of autologous pericardium.

Many materials such as autologous, synthetic, or biological patches have been used as patch material in patients undergoing CEA (4). Although the great saphenous vein has some theoretical advantages such as being an autologous graft and resistant to infection, undesirable complications such as harvesting site complications, pseudoaneurysm, or rupture have been reported, albeit not with statistically significant results (4,16). Biologically, bovine pericardium is a material that has been used for a long time in cardiac surgery. It has been reported that CEA has similar results with other patch materials in terms of restenosis and stroke in the long term. In addition, it has been suggested that it has a comparable cost to other alternative patching techniques due to its low postoperative bleeding rate and very low risk of infection (17). Synthetic patches are materials that have been used for years in CEA operations (4). Dacron patch is a polyester fiber with high tensile strength. When Dacron patch and other synthetic materials were compared, the risk of early thrombosis and restenosis was higher in the Dacron patch group; therefore, it was thought that it may have caused an increase in perioperative stroke and transient ischemic attacks. However, these outcomes were not statistically significant (4). In a meta-analysis, no statistical difference was found between synthetic, autologous vein, or bovine pericardial patches in terms of early and long-term outcomes (18). Furthermore, other important long-term sequelae associated with synthetic patches are pseudoaneurysm formation and infection development. However, these are very rare and treatable complications (19). Dacron patch is mostly used in our clinic in patients undergoing isolated CEA. In our study, Dacron patch and pericardial patch were compared in patients who were operated concurrently with CABG. One of the reasons for this is the use of Dacron patch as a carotid patch in almost all patients whose data were available. Another reason was to compare the results of patients using autologous pericardial patches with a more homogeneous patient group. There was no difference between groups in the early and late postoperative periods, except for drainage from the carotid region. The amount of bleeding in the autologous pericardium group was significantly lower than the patient group in which Dacron patch was used. In one patient in the Dacron patch group, the patient was reoperated due to bleeding from the suture line.

There are some limitations of our study. Our main limitation is that it is retrospective and the number of patients is small. However, we think that the results of our study will contribute to the literature because combined carotid artery surgery and CABG are performed less than those performed in isolation. Another limitation is that the autologous pericardial patch has not been compared with other used patch materials in the literature. Since the patches used other than Dacron patches were very limited in this patient group, these patients were excluded from the study in order not to cause heterogeneity in the patient population.

In conclusion, we consider that the use of autologous pericardium as a carotid artery patch is a safe, feasible, and effective method in patients undergoing combined carotid artery and coronary bypass surgery since it is resistant to infection, has a low postoperative bleeding profile, and is sterile, not immune-reactive, biocompatible, and an easily available low-cost material. Large scale prospective, randomized studies are needed to confirm our study results.

**Declaration of conflicting interests:** The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

**Funding:** The authors received no financial support for the research and/or authorship of this article.

## References

1. Drakopoulou M, Oikonomou G, Soulaïdopoulos S, Toutouzias K, Tousoulis D. Management of patients with concomitant coronary and carotid artery disease. *Expert Rev Cardiovasc Ther* 2019; 17:575-583.
2. Kiernan TJ, Taqueti V, Crevensten G, Yan BP, Slovut DP, Jaff MR. Correlates of carotid stenosis in patients undergoing coronary artery bypass grafting- a case control study. *Vasc Med* 2009;14: 233-237.
3. Wanamaker KM, Moraca RJ, Nitzberg D, Magovern GJ Jr. Contemporary incidence and risk factors for carotid artery disease in patients referred for coronary artery bypass surgery. *J Cardiothorac Surg* 2012;7:78.
4. Orrapin S, Benyakorn T, Howard DP, Siribumrungwong B, Rerkasem K. Patches of different types for carotid patch angioplasty. *Cochrane Database Syst Rev* 2021;2:CD000071.
5. Başar V, Hançer H. Usage of Autologous Pericardium as an Alternative Carotid Patch in Concomitant Carotid Endarterectomy and Coronary Artery By-Pass Graft Surgery. *Bozok Med J* 2019; 9:58-63.
6. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U. 2018 ESC/EACTS Guidelines on myocardial revascularization [published correction appears in *Eur Heart J* 2019;40:87-165.
7. Naylor AR, Ricco JB, de Borst GJ, et al. Editor's Choice - Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;55:3-81.
8. Akay T. Karotis arter darlıkları. In: Bozkurt AK, editor. *Periferik Arter ve Ven Hastalıkları. Ulusal Tedavi Kılavuzu İstanbul: Bayçınar Tıbbi Yayıncılık.* 2021:100-130.
9. Ozaki S, Kawase I, Yamashita H, et al. A total of 404 cases of aortic valve reconstruction with glutaraldehyde-treated autologous pericardium. *J Thorac Cardiovasc Surg* 2014;147:301-306.
10. Illuminati G, Ricco JB, Caliò F, et al. Short-term results of a randomized trial examining timing of carotid endarterectomy in patients with severe asymptomatic unilateral carotid stenosis undergoing coronary artery bypass grafting. *J Vasc Surg* 2011;54:993-999.
11. Chan JSK, Shafi AMA, Grafton-Clarke C, Singh S, Harky A. Concomitant severe carotid and coronary artery diseases: a separate management or concomitant approach. *J Card Surg* 2019;34:803-813.
12. Filová E, Staňková L, Eckhardt A, et al. Modification of human pericardium by chemical crosslinking. *Physiol Res.* 2020;69:49-59.
13. Jayakrishnan A, Jameela SR. Glutaraldehyde as a fixative in bioprostheses and drug delivery matrices. *Biomaterials* 1996;17:471-484.
14. Lee C, Lim HG, Lee CH, Kim YJ. Effects of glutaraldehyde concentration and fixation time on material characteristics and calcification of bovine pericardium: implications for the optimal method of fixation of autologous pericardium used for cardiovascular surgery. *Interact Cardiovasc Thorac Surg* 2017;24:402-406.
15. Kapisız NS, Kapisız HF, Doğan OV, Dolgun A, Yücel E. Glutaraldehyde fixation of autologous pericardial patches. *Trakya Univ Tıp Fak Derg* 2008;25:124-129.
16. Gaunt ME, Thompson M, White S, Naylor AR, Bell PR. Vein-patch rupture after carotid endarterectomy: an avoidable catastrophe. *Br J Surg* 1993;80:1490-1491.
17. Oldenburg WA, Almeray T, Selim M, Farres H, Hakaim AG. Durability of Carotid Endarterectomy with Bovine Pericardial Patch. *Ann Vasc Surg* 2018;50:218-224.
18. Texakalidis P, Giannopoulos S, Charisis N, et al. A meta-analysis of randomized trials comparing bovine pericardium and other patch materials for carotid endarterectomy. *J Vasc Surg* 2018;68:1241-1256.
19. Muto A, Nishibe T, Dardik H, Dardik A. Patches for carotid artery endarterectomy: current materials and prospects. *J Vasc Surg* 2009;50:206-213.