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Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey Phone: +90 (212) 621 99 25 Fax: +90 (212) 621 99 27
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Administration Office

Şair Eşref Bulvarı, 1402 Sk. No: 2/2 Özbaş Apt.
Alsancak / Izmir / Turkey

Phone: + 90 232 464 19 63 / **Fax:** +90 232 464 24 70

e-mail: info@oztekinoto.com | info@tksv.com

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Book: Baue AE, Geha AS, Hammond GL, Laks H, Naunheim KS. Gleen's thoracic and cardiovascular surgery. 1st ed. London: Appleton&Lange; 1991.

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Conference Paper: Davis L, Lee M, Sheridan B, et al. Berlin Heart EXCOR support in the first year of life. In: 32nd EACTS Annual Meeting; 18-20 October, 2018; Milan, Italy.

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Correspondence

Heart and Health Foundation of Turkey

Address: Şair Eşref Bulvarı, 1402 Sk. No: 2/2 Özbaş Apt. Alsancak - İzmir - TÜRKİYE

Phone: +90 232 464 19 63

Fax: +90 232 464 24 70

E-mail: info@tksv.com

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Research Article

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Restenosis Rates After Carotid Endarterectomy with Primary Closure Under Regional Anesthesia: Results of a Single Center Study with 553 Patients

İbrahim Erdinç[1], Fulya Yılmaz[2], Koray Baş[3]

[1]University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital, Department of Cardiovascular Surgery, İzmir, Turkey
[2]University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital, Department of Anesthesiology and Reanimation, İzmir, Turkey
[3]İzmir Bakırçay University Faculty of Medicine, Department of General Surgery, İzmir, Turkey

Abstract

Objectives: Carotid endarterectomy (CEA) is the current gold standard management for carotid artery stenosis but there is still a debate on which closure technique is superior to lower postoperative restenosis rates. The aim of this retrospective study is to assess "restenosis rates" of our 553 patients who underwent CEA "under regional anesthesia" with "primary closure" technique.

Materials and Methods: We retrospectively evaluated patients who underwent CEA, by non-shunting technique under regional anesthesia, with primary longitudinal arteriotomy closure between 2008 and 2019.

Results: Five hundred and fifty three patients (409 male and 144 female) were evaluated. There were no statistically significant differences in terms of demographic characteristics, sides of stenosis, operation time, preoperative stenosis ratio, and postoperative hospital stay between the gender groups. None of the patients developed restenosis (stenosis rate of over 50%) after primary closure under regional anesthesia during the two-year follow-up period.

Address for Correspondence: Fulya Yılmaz, University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital, Department of Anesthesiology and Reanimation, İzmir, Turkey
e-mail: fulya.dr@gmail.com **ORCID:** orcid.org/0000-0002-6901-7404
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Conclusion: According to our results, CEA with "primary closure under regional anesthesia" is a safe and effective surgical treatment for carotid stenosis without postoperative restenosis. We thought that further studies, which investigate the rate of restenosis after CEA, should also evaluate the "type of the anesthesia management" as a factor on it.

Keywords: Carotid artery stenosis, carotid endarterectomy, primary longitudinal arteriotomy closure, patch closure, postoperative restenosis, cervical plexus block

Introduction

Carotid endarterectomy (CEA) is the current gold standard management in reducing the risk of stroke in both symptomatic (significant stenosis >70%) and well selected asymptomatic patients with internal artery stenosis[1-10]. Currently, there are two surgical approaches in the literature: Traditional endarterectomy with longitudinal arteriotomy and the eversion technique[3]. In terms of closure techniques after CEA, there are also two options: primary closure (PRC) and patch closure (PAC) by saphenous vein or a synthetic material[3,6]. While a theoretical advantage of PAC is the reduction of the rate of re-stenosis, its disadvantages include longer carotid cross-clamping time and possible morbidities associated with vein harvesting including hemorrhage and/or infection on surgical site. On the other hand, PRC and proper medical management may be equally effective in preventing recurrent stenosis and has the advantage of reduced operative time[1].

The aim of this retrospective study is to assess restenosis rates of patients who underwent CEA under regional anesthesia with primary closure between 2008 and 2019.

Materials and Methods

We retrospectively evaluated 553 patients, who underwent CEA by non-shunting technique under regional anesthesia with primary-longitudinal arteriotomy- closure due to carotid artery stenosis between 2008 and 2019, in terms of demographic characteristics, co-morbidities, preoperative and postoperative stenosis ratio, operation time, hospital stay, and post-CEA restenosis.

Patient Selection for Operation and Management of Postoperative Anticoagulant Treatment in Our Institution

In more than 70% of asymptomatic patients and over 60% of symptomatic patients, stenosis was determined as an indication for surgery. In patients with bilateral carotid artery stenosis, symptomatic side was firstly operated in symptomatic patients and the side with higher grade stenosis was firstly operated in asymptomatic patients was. In asymptomatic patients, their medical treatment was started after the diagnosis and they were operated as soon as possible. On the other hand, symptomatic patients were operated within 15 days after the diagnosis under medical therapy. If the patients had high grade stenosis or neurologic deterioration due to cerebral hypoperfusion, they were operated urgently.

Since the patients were awake and conscious in the early postoperative period, after control of bleeding and hematoma within 2 hours after the surgery, clopidogrel 75 mg and acetylsalicylic acid 100 mg were given per oral, and heparin infusion (500 IU/hour) was started and continued approximately for 6-7 hours. Then, patients were evaluated again for bleeding and clopidogrel 75 mg and acetylsalicylic acid 100 mg heparin was increased to 7500-1000 IU and continued for 18-24 hours.

Anesthetic Management

No premedication was administered on the day of the surgery. In the operating room, a peripheral venous line was established and a standard monitorization, including a peripheral pulse-oximetry, a 3-lead electrocardiography

and a contralateral intra-arterial blood pressure monitoring, was applied.

Deep Cervical Plexus Block (C2-C3-C4) combined with Superficial Cervical Plexus Block

The anatomical landmarks were identified and marked on the skin as sternocleidomastoid muscle (SCM), cricoid cartilage, and mastoid process. After skin preparation, deep cervical plexus blocks were performed with 5 mL of the combination of 2.5 mL of 0.5% bupivacaine and 2.5 mL of 2% prilocaine near each sensory branch of nerve roots of C_2, C_3, C_4. Then, superficial cervical plexus block by 10 mL of the combination of 5 mL 0.5% bupivacaine and 5 mL 2% prilocaine was applied at the level of the 6th cervical vertebra by conventional technique.

Surgical Technique

After performing a parallel incision to SCM, the External Carotid Artery (ECA) and Common Carotid Artery (CCA) were dissected and suspended by tapes. Then, patient was given 5000 IU heparin intravenously before clamping of the carotid artery. After clamping of the artery, consciousness and motor status of patient were tested. If there was no change in the status of patient, endarterectomy was performed. At the end of the procedure, the incision was closed primarily with 6-0 polypropylene suture.

Follow-up

Patients were regularly followed up in outpatient clinics every 6 months for two years after the operation. Carotid duplex ultrasound was performed in every follow-up visit on all patients. Carotid stenosis ratio over 50% was accepted as "restenosis" after CEA surgery.

Statistical Analysis

Statistical data analysis was performed by SPSS version 21 software (SPSS, Inc., Chicago, IL, USA). Numerical data were given as mean ± standard deviation and were analyzed using the Student's t-test. $p<0.05$ was considered statistically significant.

Results

Five hundred and fifty-three patients underwent unilateral CEA due to unilateral or bilateral carotid artery stenosis by the same surgery and anesthesia team between 2008 and 2019. The rates of male and female patients were 74% (n=409) and 26% (n=144), respectively.

Preoperative duplex ultrasound evaluations of patients revealed that there was stenosis on the left side in 282 patients (211 male, 70 female) and on the right side in 272 patients (198 male, 74 female). Demographic characteristics, preoperative stenosis ratio, perioperative surgical time and postoperative hospital stay are shown in Table 1. Comorbidities of patients according to gender is shown in Table 2. There were no statistically significant

Table 1. Demographic characteristics, preoperative stenosis ratio, perioperative surgical time and postoperative hospital stay of the patients

	Male (n=409)	Female (n=144)	p-value
Age	67.04±8.76	67.88±9.40	0.612
Preoperative stenosis rate (%)	76.31±10.19	75.89±10.25	0.957
Surgical time (min)	58.78±12.26	60.99±12.69	0.193
Post-operative hospital-stay (day)	3.55±1.57	3.45±1.70	0.422

Table 2. Comorbidities of the patients according to gender

	Hypertension	Hyperlipidemia	Diabetes mellitus	Smoking
Male (n=409)	318	325	292	306
Female (n=144)	97	110	52	85

differences in terms of demographic characteristics, operation time, preoperative stenosis ratio, and postoperative hospital stay between the gender groups.

After the administration of systemic IV heparin (5000 IU), distal part of the ICA was subsequently clamped and neurological examination was performed. Consciousness, orientation, and cooperation with verbal stimuli were evaluated in patients under regional anesthesia. The patient was asked to move the contralateral upper and lower extremities, and the neurological examination was continued for 2-3 minutes[11]. Five patients required intraoperative shunt insertions due to immediate deterioration of the consciousness after carotid clamping. Three patients developed localized hematoma after the surgery that necessitated decompression surgeries.

No mortality and mortality were noticed due to operation in postoperative period. Five patients that required intraoperative shunt insertions during the surgery were evaluated by neurology doctors postoperatively. No permanent sequelae were observed in patients and they were advised to continue the appropriate medical treatments. None of the patients developed restenosis (stenosis rate over 50%) during the two-year follow-up period after the surgery.

Discussion

Although many studies have demonstrated that CEA is efficient to prevent stroke in symptomatic and well-selected asymptomatic patients, there is still a debate on which closure technique is superior for CEA to lower postoperative restenosis rates[1-6]. Restenosis is defined as recurrent luminal narrowing of more than 50% after surgery[7,9,10]. It can be detected by Duplex ultrasound[9,10], computed tomographic angiography, magnetic resonance angiography or conventional angiography. Duplex ultrasound scanning remains the most preferred diagnostic modality in clinical practice for screening[9]. After CEA procedure, the restenosis in the first year is mainly due to an intimal hyperplasia and later than 24 months, the progression of underlying atherosclerotic disease is a main reason[5,7,8,12].

Restenosis ratio after CEA with primary closure has been documented to vary in 1%-36% in the literature[1-4,7]. Using patch angioplasty in CEA is suggested to reduce both risks of restenosis and recurrent ipsilateral stroke[3].

Although surgical techniques such as PAC after conventional CEA have been shown by level-I evidence to decrease the incidence of restenosis after CEA, surgeons are still unwilling to adopt PAC for their routine use. How widely PAC is used in vascular surgery practice in the real-world is unknown (2010)[12]. All the studies included in these reports were performed over 20 years ago and quality of trials was generally poor[4]. Although previous studies disfavor the use of PRC for CEA because of neurologic events and restenosis rates, recent studies have changed the approach on this issue (2016)[6].

Not only surgical technique but also other unknown factors may affect the restenosis in CEA. Lammeren et al.[10] reported that asymptomatic patients had an increased risk for restenosis in the first year after CEA, compared to patients with either transient ischemic stroke or stroke. Also, they reported that early intervention (CEA within 30 days after stroke) was associated with decreased risk of restenosis. Garzon-Muvdi et al.[5] reported that although multiple factors might contribute to restenosis after CEA, the important factor that predisposed patients to restenosis after CEA was a family history of stroke. Bonati et al.[13] evaluated the restenosis and risk of stroke after stenting or endarterectomy. They reported that restenosis occurred more frequently after stenting than endarterectomy and increased the risk of ipsilateral stroke in the overall population.

Avgerinos et al.[6] compared perioperative and long-term results of different CEA closure techniques. They reported that PRC could be performed with equivalent results to other techniques. Cheng et al.[1] reported that PRC for CEA was related to low rates of restenosis and effective to prevent stroke in short terms. They also

reported that PRC had the advantage of reducing cross-clamp times and eliminating graft specific complications when compared to PAC. On the other hand, Huizing's reports were not compatible with Cheng's reports.

Huizing et al.[4] evaluated PRC and PAC in CEA for symptomatic carotid artery stenosis. They reported that selective patching could be recommended instead of routine patching for patients based on internal carotid artery diameter and other patient characteristics. Huizing et al.[2] showed that long term re-stenosis was significantly higher in PRC than in PAC in their review.

In this study, we investigated the restenosis rates of our cases by non-invasive duplex ultrasound. We performed all CEA operations under combined superficial and deep cervical plexus blocks applied by conventional method.

To the best of our knowledge, a few studies have indicated the effect of anesthesia management type on the rate of restenosis after CEA procedure. Kim et al.[14] assessed the feasibility and benefits of CEA under regional anesthesia versus general anesthesia in terms of the anesthesia method, neurological monitoring, shunt usage, and closure technique. They demonstrated that no carotid artery stenosis occurred after surgery under regional anesthesia with primary closure. Similarly, it might be claimed that performing our surgeries "under regional anesthesia" may be a factor to reduce the restenosis rates in our study. In addition, as van Lammeren et al.[10] stated, performing the surgeries on the early phase of stroke, as in our institution, may be another factor that affects our results.

Conclusion

According to our results, CEA with "primary closure under regional anesthesia" is a safe and effective surgical treatment for carotid stenosis without postoperative restenosis. We think that further studies which investigates the rate of restenosis after CEA should also evaluate the "type of the anesthesia management" as a factor on it.-

Ethics

Ethics Committee Approval: Since this retrospective study was conducted before January 2020, ethics committee approval is not required. Hospital management data usage permission certificate is available.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.E., F.Y., Concept: F.Y., K.B., Design: İ.E., F.Y., Analysis and/or Interpretation: F.Y., K.B., Literature Search: F.Y., Writing: F.Y., K.B.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Research Article

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Resistant Hypertension and Atrial Fibrillation: How Important Is the Rhythm?

Ebru İpek Türkoğlu[1], Emine Çiğdem Kırçiçeği Çiçekdağ[2], Eser Şekercioğlu[3]

[1]İzmir Kemalpaşa State Hospital, Clinic of Cardiology, İzmir, Turkey
[2]İzmir Bornova Türkan Özilhan State Hospital, Clinic of Anesthesiology, İzmir, Turkey
[3]Dataist Analytics, Dublin, Ireland

Abstract

Objectives: Resistant hypertension (RHT) identifies a high-risk population; however, the effect of concomitant atrial fibrillation (AF) in this patient group is understudied. The present study aimed to investigate the effect of heart rhythm (HR) in this population.

Materials and Methods: The study was designed as a retrospective, single-center, closed cohort archive screening study in a given time and outpatient data were reviewed. Patients with secondary hypertension, pseudo-RHT and heart failure were eliminated. Consecutive 101 RHT patients were included in the study and divided into two groups according to HR, sinus rhythm (SR) or AF. Baseline demographics were compared, and the correlation between N-terminal pro-brain natriuretic peptide (NT-proBNP), left atrial diameter (LAD) and age were investigated.

Results: When comparing RHT patients according to HR, AF patients were older (mean age: 73.5±7.6 vs. 61.7±11.2 years, $p<0.001$), LAD was larger (50.0±3.5 vs. 40.9±4.0 mm, $p<0.001$), LVEF was lower (53.5±2.7 vs. 57.3±2.8%, $p<0.001$) and they had higher levels of NT-proBNP (1704.5±868.9 vs. 330.3±394.9 pg/mL) than the RHT patients in SR. The correlation between LAD and NT-proBNP level was found only in RHT patients with SR, not with AF.

Address for Correspondence: Ebru İpek Türkoğlu, İzmir Kemalpaşa State Hospital, Clinic of Cardiology, İzmir, Turkey
e-mail: dripek73@yahoo.com **ORCID:** orcid.org/0000-0002-2321-8868
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Conclusion: The co-presence of AF in RHT may indicate an advanced stage of the disease, not a simple arrhythmia, and the patients should be treated accordingly. Likewise, present study's findings indicate the need to specify the cut-off levels of NT-proBNP in AF in the absence of heart failure.

Keywords: Resistant hypertension, heart rhythm, atrial fibrillation, NT-proBNP, left atrial diameter

Introduction

Resistant hypertension (RHT) is the lack of blood pressure control despite appropriate treatment in an adherent patient. Appropriate treatment includes minimum three antihypertensive drugs from different classes with proper dosage and one should be diuretic by the definition. For the diagnosis, secondary hypertension and the contributing factors for the treatment resistance such as sleep apnea syndrome or regular non-steroidal anti-inflammatory drug use should be excluded. Hence pseudo-RHT is not so rare mainly due to patient's nonadherence or improper blood pressure measurement, true RHT is relatively uncommon in clinical practice, with an approximate estimation of 5% of hypertensive patients, and identifies high-risk group[1,2]. Pathophysiology of RHT has not been fully solved yet; however, the effect of volume overload and aldosterone excess is already known[3]. Aging may also play an important role considering the higher prevalence of RHT in older patients[4-6]. Dilatation of left atrium (LA) is not uncommon in echocardiographic evaluation of hypertensive patients and reflects an impairment of the left ventricle diastolic functions. An important consequence of LA enlargement is the escalated atrial fibrillation (AF) risk. One of the important findings of the Framingham Study is that a five mm enlargement of LA detected by echocardiography raises AF incidence to 39%[7,8]. The relationships between AF, stroke, mortality and morbidity are well known and the vigilance is increased in the last decade. Hence the volume overload is thought very important in the RHT, several studies investigated the role of natriuretic peptides (NP), which are secreted from the heart as a result of increased pressure and volume. Two main natriuretic peptides are in clinical use; B-type and N-terminal B-type natriuretic peptide (BNP and NT-proBNP) and both give important prognostic information in multiple clinical scenarios beyond their role in volume homeostasis[9]. Although echocardiographic parameters, natriuretic peptides and co-morbid situation in RHT have been investigated previously, the interaction of heart rhythm with RHT is still understudied. With the aging of population and growing number of AF-patients, the topic becomes more popular. The present study aimed to compare RHT patients according to their heart rhythm and investigate the interaction of AF and RHT.

Materials and Methods

The outpatient data of our hypertension clinic were screened for the first 9 months of year 2015. Hence the clinic serves as the single second stage healthcare provider in a closed area with more than 100,000 residents, the data are considered as closed cohort data. The hospital communication system (HCS) records, which provided data about admission features such as initial complaint, personal history, blood tests, imaging results and medications of patients, were used. In the given nine months, data of 1,254 outpatients were reviewed retrospectively through the HCS. Inclusion criteria for the present study were either the uncontrolled blood pressure despite appropriate treatment with at least three drugs at best tolerated doses including a diuretic or requirement of four or more drugs to reach target blood pressure in treatment-adherent patient with the definitive diagnosis of hypertension. Adherence was monitored through controlling the refill of prescriptions via the social health security system. The exclusion criteria were the presence of secondary hypertension or white-coat hypertension, heart failure with reduced or preserved

left ventricle ejection fraction (LVEF), and moderate to severe valvular disease, which may provoke arrhythmia and renal impairment (serum creatinine >1.5 mg/dL) or an estimated glomerular filtration rate (eGFR, calculated by the CKD-epi method) <60/mL/min, which defines Grade 3a-4 renal insufficiency. After the inclusion and exclusion criteria were applied, 101 consecutive patients with RHT were identified fit for the analysis. The data about patient demographics (age, sex, complaints at application, blood pressure), laboratory and imaging study results were collected via hospital communication system. Prescriptions and compliance for treatment were checked through the online medication link of the national social security system.

NT-proBNP was the NP of choice, because of its more stable profile, and measurements were made with the Elecsys proBNP II assay/Cobas® system from Roche Diagnostics. With the knowledge of remarkable effect of age and gender on NT-proBNP, age and gender specific upper limits of 97.5th percentile for NT-proBNP were used, as defined in the prospectus information of the Elecsys proBNP II assay.

In the statistical analysis, mean ± standard deviation and percentages were given for continuous and categorical variables respectively. All the analyses were performed with the IBM SPSS-22 software. The Pearson's correlation test was the test performed to investigate the relationships between variables. Statistical significance was considered as $p<0.05$.

As the study was planned as a retrospective survey, no informed consent was obtained. Both of the authors had no conflict of interest and no external funding was received for the study. The number of ethical approval for the study was 16-10.1/3 and it was obtained from the Clinical Research Ethics Board of Ege University School of Medicine on 22.11.2016.

Results

After applying all the inclusion and exclusion criteria to 1,254 patients through HCS in the first 9 months of 2015, 101 consecutive patients were identified as true RHT, with an incidence of 8.05%. The most frequent complaints on application reports were exercise intolerance and fatigue. Among 101 patients, 31 (30.7%) were male and 70 were female with a mean age of 64.9±11.6 years. Appropriate doses of either angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus diuretic were included in the prescription of all patients. Beta-blockers in 30 patients and calcium antagonists in 26 patients were third drug of choice. Forty-five patients needed four or more drugs. Twenty-seven patients were type 2 diabetic and none of them received any glitazone treatment. Only three patients were on intensive insulin treatment. The mean blood pressure was 170.4±19.8 mmHg systolic and 101.8±91.2 mmHg diastolic. The electrocardiographic and echocardiographic reports were obtained from HCS. Left ventricle hypertrophy (LVH) and diastolic dysfunction were present in all of RHT patients. The mean LVEF was 56.3±3.3% and the mean LAD was 43.4±5.6 mm. The mean creatinine was 1.0±0.2 mg/dL and NT-proBNP 697.6±826.7 pg/mL in the study group. Descriptive demographics of the group are given in Table 1.

After the definition of the basal demographics of the study population, RHT patients were grouped based on sinus rhythm (SR) or AF. The numbers of RHT patients in the AF-group and in the SR-group were 27 and 74, respectively. The AF group was older (73.5±7.6 vs. 61.7±11.2 years, $p<0.001$), with a higher heart rate (85.3±16.8 vs. 72.7±11.8 bpm, $p<0.001$), larger LAD (50.0±3.5 vs. 40.9±4.0 mm, $p<0.001$), lower LVEF (53.5±2.7 vs. 57.3±2.8%, $p<0.001$) and higher NT-proBNP level (1704.5±868.9 vs. 330.3±394.9 pg/mL, $p<.001$) than the SR-group. Both groups had similar blood pressure levels. Although creatinine was higher in AF -patients (1.1±0.2 vs. 0.96±0.2 mg/dL, $p=0.004$), other blood results remained alike in both groups. Hence all the eGFR results were defined as >60 ml/min (absence of renal failure), a comparison between the groups were not made. Antihypertensive medication was similar in both groups (all the patients with AF and SR did received appropriate dosage of a RAS blocker, either ACEİ or ARB with diuretic); however, AF patients tended to receive

Table 1. Group demographics

	RHT patients (n=101)
Gender	Male: 30.7% (n=31)
	Female: 69.3% (n=70)
Age (years)	64.91±11.63
HR (bpm)	76.11±14.43
SBP (mmHg)	170.48±19.85
DBP (mmHg)	101.83±91.26
NT-proBNP (pg/mL)	697.68±826.73
LAD (mm)	43.40±5.65
LVEF (%)	56.34±3.31
Ascendan aorta diameter (mm)	35.48±3.66
Fasting glucose (mg/dL)	119.66±41.42
Urea (mg/dL)	36.91±13.00
Creatinine (mg/dL)	1.00±0.23
Potassium (mmol/L)	4.40±0.46
LDL (mg/dL)	112.27±35.61
TG (mg/dL)	158.45±72.21
CRP (mg/dL)	4.97±5.23

RHT: Resistant hypertension, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LAD: Left atrial diameter, LVEF: Left ventricle ejection fraction, LDL: Low-density lipoprotein, TG: Triglyceride, CRP: C-reactive protein, NT-proBNP: N-terminal pro-brain natriuretic peptide, n: Number

more b-blockers than the patients in SR (24/27 vs. 51/71 patients, p=0.038). Comparison of two groups is given in Table 2.

In the third part, the relationship between NT-proBNP and some clinical variables was investigated in both groups. In the SR-group, NT-proBNP and left atrial diameter (LAD) were correlated (pairwise r=0.451, p<0.001), and the correlation continued even partially (r=0.234, p<0.049) after being controlled for variables known or thought to be related to NT-proBNP such as age, sex, heart rate, systolic and diastolic blood pressures. On the contrary, in the AF-group, no correlation was found between NT-proBNP and LAD, neither pairwise nor partial (respectively r=0.208, p=0.297 and r=0.330, p=0.134, after controlling same variables as age, sex, HR, SBP and DBP). Similar relationships were obtained while searching the correlations between NT-proBNP and age in both groups. In RHT patients with SR, there was a significant partial (after controlling for LAD, gender, HR, SBP and DBP) as well as pairwise correlation between NT-proBNP and age, which looked significant only in pairwise analysis. After controlling the variables, the

Table 2. Two groups are defined according to the heart rhythm in the RHT population and the comparison of two groups

Rhythm	AF (n=27)	SR (n=74)	p-value
Gender	M (5) 18.5%	(26) 35.1%	0.109
	F (22) 81.5%	(48) 64.9 %	
Age (years)	73.56±7.62	61.76±11.27	**<0.001**
HR (bpm)	85.33±16.88	72.74±11.87	**<0.001**
SBP (mmHg)	164.78±17.98	172.55±20.21	0.081
DBP (mmHg)	125.19±175.31	93.31±13.74	0.121
NT-proBNP (pg/mL)	1,704.59±868.19	330.30±394.96	**<0.001**
LAD (mm)	50.07±3.55	40.96±4.09	**<0.001**
LVEF (%)	53.52±2.71	57.36±2.89	**<0.001**
Ascendan aorta diameter (mm)	35.67±3.54	35.41±3.73	0.753
Fasting glucose (mg/dL)	117.89±32.88	120.31±44.31	0.796
Urea (mg/dL)	40.67±12.19	35.54±13.10	0.079
Creatinine (mg/dL)	1.10±0.25	0.96±0.21	**0.004**
Potassium (mmol/L)	4.54±0.46	4.34±0.46	0.055
LDL (mg/dL)	106.38±31.49	114.37±36.94	0.328
TG (mg/dL)	140.22±74.08	165.19±70.84	0.125
CRP (mg/dL)	4.61±6.50	5.06±4.91	0.775

The values are given as mean ± standard deviation. Significant p-values are shown in bold.
RHT: Resistant hypertension, HR: Heart rate, AF: atrial fibrillation, SR: sinus rhythm, M: Male, F: Female, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NT-proBNP: N-terminal pro-brain natriuretic peptide, LAD: Left atrial diameter, LVEF: Left ventricle ejection fraction, LDL: Low-density lipoprotein, TG: Triglyceride, CRP: C-reactive protein, n: Number

partial correlation between NT-proBNP and age became not significant. In contrary, the AF-group represented not any significant relationship between NT-proBNP, age or LAD. Results are given in Table 3.

Discussion

Hypertension (HT) and AF are two important problems of daily clinical practice and they often coexist[10]. While the Framingham data suggest that hypertension might foretell AF, the 15-year follow-up data of the study indicate that more effective BP control does not reduce AF occurrence in the hypertensive patients[8,11]. Although the relationship between HT and AF is well established, the underlying mechanism is not been completely solved[10]. Aldosterone excess, HT and AF may be related in multiple ways. The activation of renin-angiotensin system increases aldosterone synthesis and increased aldosterone levels are associated with HT, AF, LVH, and diastolic dysfunction in general population[12]. Aldosterone endorses myocardial remodeling and AF. Hence AF develops, it further increases aldosterone level creating a vicious circle[13]. Whether the AF-risk increases linearly with BP or there is a BP threshold, above which the risk increases, is not known[10]. Furthermore, the blood pressure goal in this population is also uncertain although available data do not recommend lowering BP in AF patients below current targets[10,12].

HT is a modifiable cardiovascular risk factor, but treatment resistance is a real problem. Prevalence studies report the treatment resistance as 5%-30% in the hypertensive patients, which includes pseudo-resistant and treatment non-compliant patients. After applying strict definition criteria, the rate of RHT is thought to be under 10% of all patients with hypertension. RHT defines an important high-risk population for target organ injury, long-term renal disease and premature cardiovascular events mediated by hypertension[1]. The definition of resistant hypertension is basically a rule-out diagnosis. The patient, whose blood pressure is not controlled, should be adherent to treatment, the treatment should contain a combination of proper drugs in appropriate dosages, and all of the causes of secondary hypertension and treatment resistance should be excluded[1]. However, this kind of definition may put different diseases with various etiologies and underlying pathologies in the same diagnostic basket, which could lead the inappropriate treatment of individuals with similar appearance but different underlying pathophysiological mechanism.

The mechanism, which is responsible for RHT, may not be a simple single one and perhaps underlying pathophysiological causes may differ by age; however, Gaddam et al.[3] described one of them as the aldosterone excess with an increased intravascular volume. They demonstrated higher levels of NP's in RHT compared to

Table 3. The correlation between NT-proBNP, left atrial diameter and age in both groups according to the heart rhythm in RHT

		LAD		Age	
		SR	**AF**	**SR**	**AF**
NT-proBNP	**Pairwise**	**0.451 (p<0.001)**	0.208 (p=0.297)	**0.670 (p<0.001)**	0.173 (p=0.387)
	Partial	**0.234 (p=0.049)[a]**	0.330, (p=0.134)[a]	**0.590 (p<0.001)[b]**	0.183 (p=0.415)[b]
LAD	**Pairwise**	-	-	**0.469 (p<0.001)**	-0.142 (p<0.001)
	Partial	-	-	0.175 (p=0.151)[c]	-0.246 (p=0.269)[c]

Pairwise correlation coefficients are Pearson's r; [a]: Controlling for Age, Gender, HR, SBP, DBP, [b]: Controlling for LA, Gender, HR, SBP, DBP, [c]: Controlling for BNP, Gender, HR, SBP, DBP.
Significant p-values are shown in bold.
NT-proBNP: N-terminal pro-brain natriuretic peptide, RHT: Resistant hypertension, LAD: left atrial diameter, SR: sinus rhythm, AF: atrial fibrillation, BNP: brain natriuretic peptide, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

controls, which was more pronounced in male gender[3]. The correlation between NPs and adverse cardiac outcomes is well known, and because of that, NPs are utilized in many clinical scenarios to identify high-risk patients beyond their role in volume homeostasis[9]. Defining the upper limits of normal is also not so simple for NT-proBNP considering the important impact of age and gender. Previously underlined 125 pg/ml level of NT-proBNP is basically a rule-out level for acute heart failure derived mainly from the PRIDE-study and it may be improper to use a rule-out level for any rule-in process[14,15]. New European NP guideline has changed the rule-in levels for heart failure in accord with FDA recommendations; however, it may also be improper to use any heart failure rule-in level for the diagnosis of hypervolemia[16]. A former paper of us on RHT, which used gender and age specific cut-offs for NT-proBNP in the 97.5th percentile, suggested that high levels of NT-proBNP did not exist in every RHT patients. The study suggested only the elderly patients with RHT had higher levels of NT-proBNP, which may indicate high risk of adverse events as well as hypervolemia[17]. Considering not all but elderly RHT patients have higher levels of NT-proBNP, a speculation can be made that these patients might be at greater risk for AF because of volume overload and higher risk, which is assigned by elevated levels of NT-proBNP and age. Identifying the high-risk patients is crucial for an accurate approach. Although RHT population is studied widely, the impact of rhythm in this population is not well described. As the number of patients with AF is growing each day and AF burden becomes a real clinical issue, as a subgroup, RHT patients with AF are not defined decently. The present study investigated RHT patients of a closed cohort and compared the features of these patients according to their rhythms. RHT patients with AF were older, which is consistent with the knowledge of increasing prevalence of AF with aging[18]. This finding also might indicate that the development of AF in RHT patients addresses the disease advance in years; however, whether all the patients would develop AF with aging or which patients would develop AF in years and what could be done to prevent it are not completely known yet. In the present study group, RHT patients in AF had higher HR, NT-proBNP and creatinine levels, larger LAD and lower LVEF than RHT patients in SR, which might be related to a more advanced phase of the disease. Higher creatinine levels, which may indicate deteriorating of renal function, larger LAD and lower LVEF can be attributed directly to the AF, because the interaction between AF and renal function is well known as the cardiac function[18]. Hence the relationship of AF and NT-proBNP is recognized well for years, the higher level of that biomarker in atrial fibrillation group has been found not to be surprising. Several studies have suggested that the NT-proBNP levels of 800-1100 pg/mL should be accepted as a median in patients with atrial fibrillation and preserved left ventricle ejection fraction. Not any correlation of biomarker with duration of AF or LAD is found[19]. Uncontrolled blood pressures may lead AF, and also as a marker, high plasma levels of NT-proBNP can predict future onset of AF independently[18,20]. Uncontrolled blood pressure over years and also increased NT-proBNP levels in resistant hypertensive patients may explain high percentage of AF patients in RHT group. It may give rise to the thought that older RHT patients having increased levels of NT-proBNP would develop AF over years if the blood pressure could not be controlled well and required precautions are not taken. The present study found a relationship between NT-proBNP, LAD and age, in resistant hypertensive patients only on sinus rhythm but not on atrial fibrillation. The lack of correlation in the AF-group may be due to that all patients have higher levels of that biomarker and larger LAD. This finding may mean that current cutoffs for NT-proBNP may not be appropriate for patients with AF, and AF-specific cutoffs are needed for these patients.

Study Limitations

The most important limitation of the study is its retrospective design. Single center design is another limitation, which led to limited number of patients, although the data of a closed cohort were used. Using ambulatory blood pressure holter instead of the office-

based BP levels could be much better even the blood pressures were measured according to the guidelines by a hypertension-nurse well educated in this area. The prescription information and treatment adherence of patients were checked via online social security system, but it is always possible that patients did not take the pills regularly even the pills were refilled. Despite these limitations, the study presents real-world clinical data and compares RHT patients according to their rhythm, while questioning the effect of rhythm in RHT population, which represents a growing and understudied part of hypertensive patients.

Conclusion

Resistant hypertension, elevated levels of NT-proBNP and atrial fibrillation are important parts of a daily clinical dilemma, where age plays a fundamental role. In our aging society, with the longer expectation of survival, the borders between cardiovascular diseases become hazy. The present study suggests that uncontrolled BP and high NT-proBNP levels may lead or foretell AF development in RHT patients over years, and the elderly RHT patients with elevated levels of NT-proBNP should be monitored closely for the development of AF and every precaution should be taken to prevent it. Once AF develops, these patients differ from the patients in SR, which might be speculated as transition to a more advanced phase of the disease or another disease. The positive correlation between NT-proBNP and LAD is found only in RHT patients with SR, but not with AF, which may indicate the need for specific cut-off levels of NT-proBNP in AF.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Board of Ege University School of Medicine on 22.11.2016 (no: 16-10.1/3).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception and Design: E.İ.T., E.Ç.K.Ç., E.Ş., Acquisition of Data: E.İ.T., E.Ç.K.Ç., Analysis and/or Interpretation of Data: E.İ.T., E.Ş., Drafting of the Manuscript: E.İT., Critical Revisions: E.İ.T., E.Ç.K.Ç., E.Ş., Statistical Analysis: E.Ş., Technical and Material Support: E.İ.T., E.Ç.K.Ç., Supervision: E.İ.T.

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Use of a Vascular Closure Device (AngioSeal) in Endovascular Interventions Performed Through the Popliteal Artery Due to Iliofemoral Artery Occlusion

Emced Khalil

Ordu University Training and Research Hospital, Department of Cardiovascular Surgery, Ordu, Turkey

Abstract

Objectives: We aimed to evaluate the results of the use of AngioSeal in endovascular interventions performed through the popliteal artery access as a consequence of occlusive disease in the iliofemoral artery.

Materials and Methods: This case series was conducted at Ordu University Training and Research Hospital between June 1, 2020 and August 31, 2020. All endovascular interventions that were performed via popliteal artery puncture followed by AngioSeal application during the relevant dates were included in the study.

Results: 77.3% of the 22 cases were male, the mean age was 66.64±12.73 (minimum-maximum: 40-89), and 59.1% of the patients were smokers. Endovascular treatment indications were resting pain (in 54.5%) and claudication (in 45.5%). No major complications developed after the procedures, but a single case with minor complication (hematoma <3 cm) was recorded. Procedural success was achieved in 90.9% of patients. There were two unsuccessful cases, one was a 75-year-old male and the other was a 65-year-old female. Both were non-smokers and had diagnoses of hypertension and coronary

Address for Correspondence: Emced Khalil, Ordu University Training and Research Hospital, Department of Cardiovascular Surgery, Ordu, Turkey

e-mail: emjedkhalil@gmail.com **ORCID:** orcid.org/0000-0003-1050-2656

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artery disease. While the target lesion location was mid + proximal superficial femoral artery (SFA) in the female patient, it was SFA + iliac artery in the male patient.

Conclusion: When AngioSeal is used to provide hemostasis after popliteal artery puncture in endovascular interventions, success rate and patient comfort are highly satisfactory. In addition, the incidence of complications after the procedure is quite low.

Keywords: Vascular closure device, hemostasis, ambulation, peripheral arterial disease

Introduction

Peripheral artery disease can be defined as the atherosclerotic or thrombotic disease of arteries other than the coronary artery and aorta[1]. Lower extremity artery disease is characterized by the involvement of the iliac and/or distal arteries. It may present with different clinical manifestations, including asymptomatic presentation, intermittent claudication, resting pain, acute leg ischemia and chronic leg-threatening ischemia. Lower extremity arterial disease is closely associated with increased cardiovascular events, including patients without symptoms[1,2]. Treatment of peripheral arterial disease consists of preventive measures and exercise, and also interventional and surgical treatment. Today, with the advances in devices and the increase in operator experience, endovascular interventions (depending on the localization of the lesion, its length and the surgical risk of the patient) have gained an important place in the treatment of symptomatic peripheral arterial disease[3].

Complications such as bleeding, hematoma, pseudoaneurysm, and vascular occlusion may occur after endovascular treatment, resulting in increased treatment costs, hospital stay, and workload. Some of these complications are directly related to the treatment and some of them are related to the arterial access site[4,5]. After interventional vascular procedures, hemostasis has traditionally been achieved by manual compression (MC). Recently, vascular closure devices (VCD) for hemostasis have gained popularity after endovascular procedures[6,7]. Compared to MC, patients receiving VCD have reduced hemostasis time and pain, without increased risk of complications, thereby shortening time until ambulation[6,7]. Different systems for vascular access site closure have been developed, including suture closure systems (Perclose Abbott, Super Stitch Sutura), clip application systems (StarClose 6F Abbott, Angiolink Medtronic), and plugging systems (AngioSeal Saint Jude, Vasoseal Datascope)[8].

In cases where the common femoral artery or the superficial femoral artery (SFA) cannot be used effectively (in the presence of non-palpable artery, severe calcification, graft prostheses, high femoral bifurcation, previous operation scar or obesity), the popliteal artery (PA) can be preferred as an access site for endovascular treatment[9]. PA access has limitations such as requiring prone position and ultrasonographic guidance[10]. There are very few studies that have published the results of VCD use in PA-access interventions, but the authors have mostly reported successful results[11-14]. To our knowledge, there is no comprehensive study reporting the results of AngioSeal use in endovascular interventions with PA access. In this study, we aimed to evaluate the results of AngioSeal use in endovascular interventions performed through the PA access due to the presence of occlusive disease in the iliofemoral artery.

Materials and Methods

This case series study was conducted at Ordu University Training and Research Hospital between June 1, 2020 and August 31, 2020. Ethical approval was obtained from the Ordu Universty Clinical Ethics Committee (no: 2021/183).

Patients

All endovascular interventions performed via popliteal artery puncture followed by AngioSeal use during the relevant dates were evaluated for eligibility to the study.

Exclusion Criteria

- History of bleeding or platelet disorder.
- Undergoing diagnostic procedures,
- Having pre-existing systemic or cutaneous infection,
- Having abnormal international normalized ratio (INR) or platelet count before the procedure,
- Presence of scar tissue at the access site.

Vascular interventions were performed in 124 cases at the relevant dates, and 22 of these cases met the inclusion criteria.

Variables

The parameters examined were as follows:

- Patient characteristics (age, gender, smoking status, comorbid diseases),
- Features of the procedure (target lesion location, indication, percentage of vascular occlusion, endpoint, complication, time to ambulation)

Procedure

Computed tomography angiography was performed in all patients before endovascular treatment. The PA access site was selected according to the lesion location and type. Following successful puncture, an 0.018-inch guidewire was advanced through the needle and manipulated into the SFA. Angioplasty procedures were carried out in a standard fashion. PA punctures were performed under ultrasound guidance by using a micro-puncture access set with a 21-gauge needle. After advancing a 0.018-inch guidewire, it was exchanged for a 6-F vascular sheath (in 45 accesses) or a 7-F vascular sheath (in 2 accesses) under fluoroscopic guidance on the patient in the prone position (Figure 1a).

After arteriography was performed and the lesion site was observed, 5000 IU/mL heparin was administered just before the intervention. After the completion of the procedure, the puncture site was closed with the use of an AngioSeal VCD (6-Fr), which constitutes an off-label use of the device. Closure was performed as follows: a guidewire, provided with the standard Angioseal set, was passed through the 6-Fr arterial sheath. Manual pressure was applied to the puncture site as the vascular sheath was removed over the wire. A 6-Fr sheath, again provided with the standard AngioSeal set, was passed over the guidewire and positioned in the artery. The anchor was set in position (by deploying the device through the sheath) and was pulled back to seal the puncture by tamping the arterial plug against the arterial wall.

The external view of the VCD application procedure is shown in Figure 1b and Figure 1c. Hemostasis usually occurs within 2-3 minutes (Figure 1d). Afterward, the patients were placed in the supine position and taken to a recovery room with standard dressing (without sandbag). Four hours of bed rest was recommended. Achieving hemostasis was accepted as procedural success. Doppler ultrasonography was performed within 4-6 hours in all patients to check the distal flow. Patients were advised to use acetylsalicylic acid (100 mg) and clopidogrel (75 mg) daily after discharge. The popliteal intervention site was examined in the outpatient clinic at the 1st week and 1st month after the intervention for the assessment of complications such as hematoma, arteriovenous fistula, or pseudoaneurysm.

Statistical Analysis

All analyses were performed on SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). For the normality check, the Shapiro-Wilk test was used. Data were given as mean ± standard deviation or median [minimum-maximum (min-max)] for continuous variables according to the normality of distribution, and as frequency (percentage) for categorical variables.

Results

Among the 22 patients included in the study, 77.3% were male and the mean age was 66.64±12.73 (min-max):

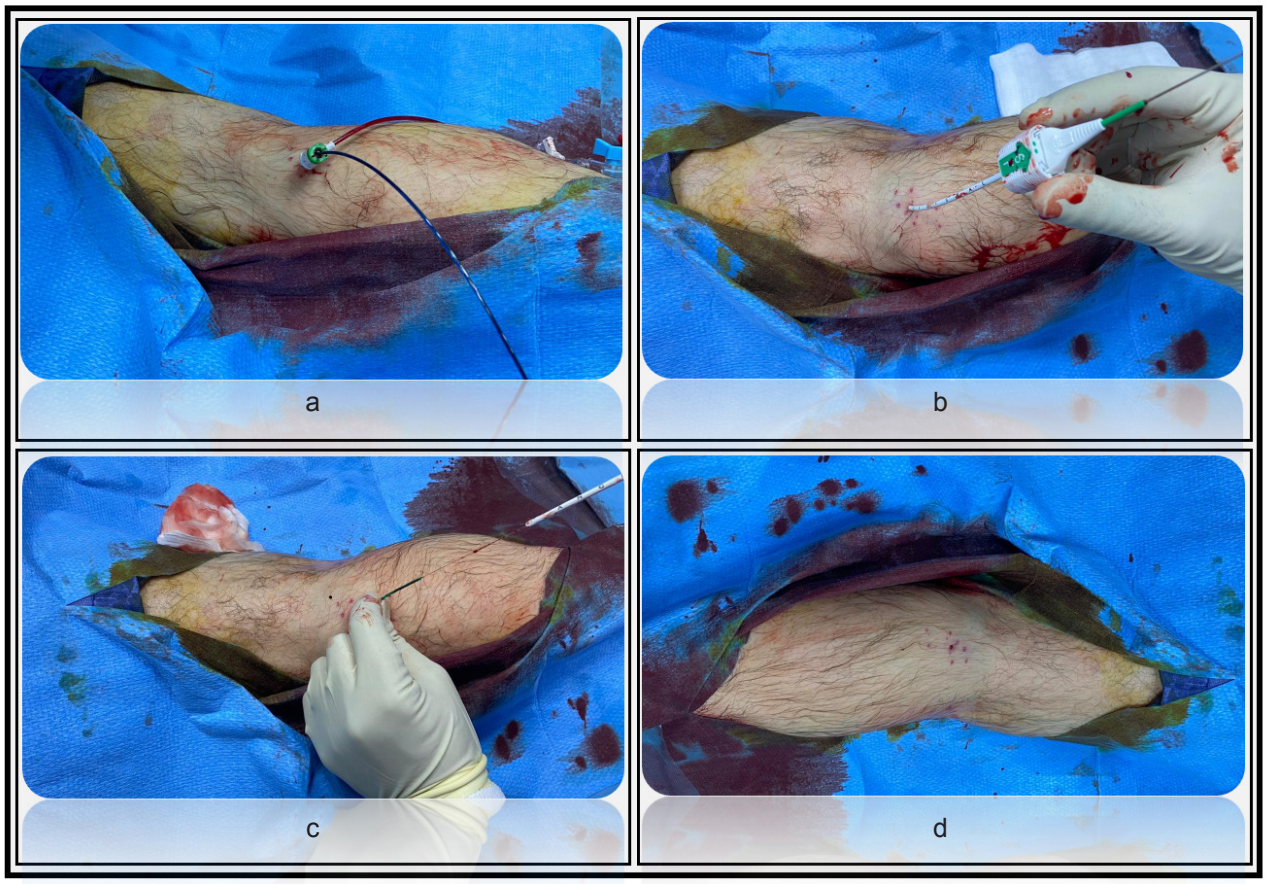

Figure 1. a) Popliteal intervention to the patient in the prone position.
b and c) AngioSeal application procedure.
The same type of Angioseal was applied to all patients. The arteriotomy was closed in all patients immediately after the operation in the interventional radiology department. A guidewire that came with the standard Angioseal package was routed through the 6-Fr arterial sheath. The vascular sheath was withdrawn over the wire, and manual pressure was applied to the puncture site. A 6-Fr sheath from the Angioseal package was passed over the guidewire and placed in the artery. After the device was deployed through the sheath, the anchor was placed. Finally, the anchor was retracted, and the puncture was closed by pressing the arterial plug toward the arterial wall.
d) Ensuring hemostasis without hematoma after the procedure

40-89 years. 59.1% of the patients were smokers. The most common comorbidities were hypertension (77.3%), diabetes mellitus (45.5%), coronary artery disease (31.8%), and hyperlipidemia (27.3%). The indications for endovascular treatment were resting pain (in 54.5%) and claudication (in 45.5%). No major complications (major hematoma, AV fistula, pseudoaneurysm, or acute lower extremity ischemia) developed after the procedures, and only one (n=1) minor complication was recorded –a case of hematoma which was <3 cm in size. The median (min-max) ambulation time of the cases was 3 (3-8) hours. Unilateral intervention was performed in all cases, except for one patient who underwent bilateral intervention.

Procedural success was identified in 90.9% of patients (in one case, the AngioSeal could not be placed completely, and in the other case, the procedure failed due to high blood pressure; 180/140 mmHg). Regarding these two cases in which the operation failed, one was a 75-year-old male and one was a 65-year-old female. The latter was the patient who had suffered from a minor hematoma.

In these two patients, hemostasis was achieved with MC after the procedure (MC durations were 15 min and 20 min, respectively). Both cases were non-smokers and had diagnoses of hypertension and coronary artery disease. While the target lesion location was mid + proximal SFA in the female patient, it was SFA + iliac artery in the male patient. The summary of patient characteristics is shown in Table 1.

Table 1. Summary of the patients' characteristics

Age (year)	**66.64±12.73**
Gender	
Male	17 (77.3%)
Female	5 (22.7%)
Smoking	
Yes	9 (40.9%)
No	13 (59.1%)
Additional disease	
Hypertension	17 (77.3%)
Diabetes mellitus	10 (45.5%)
Coronary artery disease	7 (31.8%)
Hyperlipidemia	6 (27.3%)
Chronic kidney disease	3 (13.6%)
Target lesion location	
Distal SFA	6 (27.3%)
Proximal SFA	4 (18.2%)
Mid-SFA	2 (9.1%)
Mid + proximal SFA	5 (22.7%)
SFA + Iliac artery	5 (22.7%)
Indication	
Rest pain	12 (54.5%)
Claudication	10 (45.5%)
Vascular occlusion (%)	100 (70-100)
Endpoint	
Success	20 (90.9%)
Failure	2 (9.1%)
Complication	
No	21 (95.5%)
Hematoma	1 (4.5%)
Time to ambulation (h)	3 (3-8)

SFA: Superficial femoral artery
Data are given as mean ± standard deviation or median (minimum-maximum) for continuous variables according to the normality of distribution, and as frequency (percentage) for categorical variables

Discussion

With the widespread use of endovascular interventions for treatment, different techniques have been developed and alternative options have been produced for many procedures. Some of the key differences between these options are the puncture site, the decision to use a VCD, the specific type of VCD to be used and other factors. In this study, the results of endovascular treatment interventions using PA access and AngioSeal device were evaluated in patients who had required PA access due to iliofemoral occlusive diseases. It was determined that the procedure was successful in approximately nine out of 10 cases, and there was only a single case who developed a minor complication.

The number of studies published concerning the results of endovascular treatment via PA access is very limited. As far as we know, there is no comprehensive study that has described the results of AngioSeal use in such patients. In a previous study, the authors reported that the procedures were successful and no complications developed in three cases in which they used AngioSeal after endovascular treatment via PA access[11]. The results of the use of different VCDs in interventions from popliteal puncture have also been published. In a case series of 13 cases, it was reported that the treatment was successful in all cases, and acute thrombosis developed due to incorrect intravascular deployment of the device in one of the three cases in which the ExoSeal VCD was used[12]. In another study investigating ExoSeal use with PA approach, the authors reported that they were successful in 44 of the 46 cases. Complications were present in two cases: the first was a minor hematoma (<3 cm) originating from VCD, while the other was AV fistula development[13]. A different study reported 100% success in 28 cases in which a clip device was used in endovascular treatments performed through PA access; however, the authors found that a major complication (PA occlusion) had developed in one case, and minor hematoma (<5 cm) had developed in three cases[14]. One comparative study assessing the results of using common femoral artery access and PA access for

femoropopliteal artery occlusive disease (without VCD) found that there was no significant difference between the two access sites in terms of complications, but a lower success rate was reported in PA access[15]. The lower success rate via PA access may be important when comparing treatments and the utility of VCD application from these access sites. However, the majority of the literature appears to show that interventions with PA access yield successful results and are reliable in terms of complication development[16-18]. Consistent with this evidence, in our study, it was determined that 91% of the interventions using AngioSeal were successful. We think that AngioSeal may be a preferable option if there are no contraindications for endovascular intervention via PA puncture.

In order to achieve adequate hemostasis after endovascular interventions, patients must lie in bed for a long time. This period is prolonged especially when MC and sandbags are applied, often decreasing patient comfort and increasing length of stay in the hospital, as well as causing unnecessary workload for staff[6,19-22]. The use of VCDs in endovascular interventions is very valuable in this respect, and they may benefit both healthcare providers and patients. Although this study did not include a comparative group with a different application, based on our clinical experience and the results of available studies, we believe that the time to ambulation (median: 3 hours) determined in our study was relatively short. When studies on this subject are examined, a decrease in time to ambulation has been reported after VCD use, which supports our opinion[19]. That said, currently there is no comprehensive study that has published the results of AngioSeal application after PA access. However, it has been shown in many extensive studies that the use of VCD on other access sites reduces time to ambulation by approximately 50%[6,20-22]. Thus, based on prior results and our findings, it appears that the use of AngioSeal in endovascular interventions with PA access has ideal results in terms of time to ambulation.

An indicator of success in endovascular interventions is procedure-related complications. As the risk of complications decreases, the preferability of the procedure increases. In our study, complications that developed after the intervention were recorded for this purpose. Accordingly, no major complications developed after endovascular interventions performed through the PA access site. Minor hematoma (<3 cm) was detected in only one case. In almost all of the comprehensive systematic reviews and meta-analyses, it has been shown that the most common complication after the use of AngioSeal is hematoma. In addition, it was underlined that major complications related to the AngioSeal device did not develop and that only some minor complications may be observed with the use of AngioSeal[7,22-26]. There is no agreement between published studies regarding complication frequency with VCD or MC applications after endovascular intervention. In various studies investigating complications, different outcomes have been reported; some have found VCD to be superior[22,27,28], others have found no difference[6,20,29,30], while a couple of studies have reported MC to be superior[31,32]. However, as mentioned before, there are no comprehensive reports of complications pertaining to endovascular interventions performed through PA access using AngioSeal. On the other hand, relatively low frequency of minor complications has been reported in PA-access procedures performed with other VCD devices[12-14]. In the light of our study and previous studies, interventions with PA access using AngioSeal were thought to be safe in terms of complications. In addition, low frequency of major complications was noted in studies in which only the results of MC application were published[18,33-35]. However, since there was no control group in our study, we cannot directly suggest superiority concerning this matter.

Study Limitations

The retrospective and single-center design of this study are important limitations. The relatively low number of cases evaluated in the study and the short follow-up period may have prevented the occurrence of rare complications. In studies with more participants, rare complications and related conditions may be observed. Since case groups

receiving different approaches (other VCD device or MC) were not included in our study, specific comments cannot be made for the comparison of AngioSeal with other methods of closure. Although there is no consensus on this subject, it has been shown in various studies that the development of complications after endovascular interventions may be related to patient-related characteristics, body weight, comorbidities, sheath size, some procedural features, and the experience of the clinician[32,36-41]. Since there was no control group in our study, the effect of these parameters on the results could not be examined.

Conclusion

To the best of our knowledge, this is the first study to report the clinical features of cases for which AngioSeal was used to provide hemostasis after the use of PA access for endovascular intervention (due to the presence of occlusive disease in the iliofemoral artery). No major complications occurred with the use of AngioSeal. Also, considering our clinical experience and the results of other studies, time to ambulation was shortened. In cases in which the use of SFA access is not possible, it may be preferable to utilize PA access with AngioSeal closure as demonstrated by successful results in terms of procedural success, complications, and patient comfort. In future studies, optimal intervention(s) can be determined by comparing different VCD devices and MC in patients undergoing endovascular intervention with PA access.

Ethics

Ethics Committee Approval: This case series study was conducted at Ordu University Training and Research Hospital between June 1, 2020 and August 31, 2020. Ethical approval was obtained from the Ordu Universty Clinical Ethics Committee (no: 2021/183).

Informed Consent: Informed consent was taken from all the patients.

Peer-review: Externally peer-reviewed.

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Carotid Artery Stenting Using the Double Embolic Protection Technique

Serdal Baştuğ

Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Cardiology, Ankara, Turkey

Abstract

Objectives: Severe internal carotid artery stenosis is observed in 2%-8% of the population and responsible for 20%-30% of all strokes. The reliability of carotid artery stenting in high-risk patients with high thrombus burden and vulnerable plaques and the treatment strategy in these patients remain unclear. Our aim in this study was to evaluate the short-term and long-term results of the use of double embolism protection devices in high-risk patients.

Materials and Methods: Patients who underwent carotid artery stenting between December 2016 and 2019 in our center were evaluated retrospectively. Among these patients, 17 patients in whom double embolism protection devices were used during stenting procedure were included in the study.

Results: The mean age of the patients was 76±7.1 years and 13 of them were male. All patients had hypertension and 82.3% had diabetes mellitus. All patients were symptomatic. Both distal and proximal cerebral protection devices were used together during the procedure. While no death was observed after the procedure, contralateral major stroke was observed in one patient and transient ischemic attack was observed in two patients. Restenosis was not observed in the control carotid Doppler ultrasonography, which was performed after the procedure, within the first year of follow up.

Conclusion: In this study, the feasibility and reliability of using distal and proximal cerebral protection devices together in high-risk patients were shown. Carotid stenting and double cerebral protection devices can be applied with acceptable complications in experienced centers and in suitable patients, especially in those with high surgical risk.

Keywords: Carotid artery stenting, dual protection, stroke

Address for Correspondence: Serdal Baştuğ, Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Cardiology, Ankara, Turkey

e-mail: serdalbastug@yahoo.com **ORCID:** orcid.org/0000-0002-1400-4614

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Introduction

Cerebrovascular stroke causes long-term disability. It is the third most common cause of death after cancer and cardiac-related deaths in developed countries[1]. Strokes are mainly derived from ischemic and hemorrhagic origin. Ischemic strokes are associated with carotid artery atherosclerosis, and approximately 20%-25% of patients with ischemic stroke have internal carotid artery disease. Carotid artery stenting (CAS) is a frequently used treatment modality in symptomatic or asymptomatic patients with carotid artery stenosis with low complication rates. The SAPPHIRE (Carotid stenting in high-risk endarterectomy patients) study has shown that CAS is not inferior to carotid artery endarterectomy (CEA) in high-risk patients for endarterectomy[2]. CAS-related strokes are the most feared complications that can occur. Distal and proximal cerebral protection devices are used to prevent thromboembolic complications. Distal filters are basket-shaped filters that are placed at the distal region of the lesion in the internal carotid artery and they aim to capture the debris that may be generated during stent placement. These filters are more commonly used during carotid stenting due to their relative ease of use. On the other hand, proximal cerebral protection devices are the systems in which the flow of the internal carotid artery is interrupted using a balloon, and by this way, antegrade embolisms are prevented relatively more effectively. It is aimed to prevent process-related debris with continuous aspiration during the procedure or after the balloon is deflated. Theoretically, proximal cerebral protection devices are safer because of not contacting the lesion during use. Previous studies have revealed that thromboembolic complications are observed more frequently with distal cerebral protection devices than proximal ones[3]. However, the risk of thromboembolism is much higher during the placement of thromboembolic devices in cases of tortuous carotid arteries, nearly complete occlusions, intra-plaque hemorrhage, and vulnerable thrombosed stenosis[4]. It is possible to have an idea about the risk of thromboembolism during the procedure by evaluating factors such as plaque morphology, vulnerability, ulceration, plaque calcification rate, and intra-plaque hemorrhage with imaging methods. Carotid ultrasound, positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT) are the most commonly used imaging modalities. It is not clear which method is more effective in preventing thromboembolic complications in these patients. In the present study, the short- and long-term results of the combined use of proximal and distal cerebral protection devices in symptomatic patients with carotid artery stenosis and vulnerable plaques, and the reliability and feasibility of these systems were evaluated.

Material and Methods

Study Population

Two hundred twenty-five patients who underwent CAS between December 2016 and 2019 in our clinic were investigated retrospectively. Of these, 17 patients for whom the two thromboembolism protective devices were used simultaneously were included in the study group. The results of Doppler ultrasonography (USG), MRI, or CT, which were performed to determine the plaque morphology before the procedure, and the reports of selective carotid angiography were evaluated. The grade of carotid stenosis was calculated using the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria[5]. All of the patients were symptomatic (such as transient ischemic attack, ischemic stroke, and ipsilateral amaurosis fugax) and considered to be at high risk for thromboembolic complications based on the imaging results. Revascularization strategy was determined by presenting the patients to the cardiovascular surgery and cardiology council.

The patients underwent neurological examination and written consents were obtained from the patients before the procedure. Ethical approval was obtained from the Ethics Committee of Ankara City Hospital (decision no: of E1-20-1501, date 20.01.2021). The baseline demographic characteristics, antiaggregant or anticoagulant use, history of cerebrovascular event and/or transient ischemic attack (TIA), and clinical and imaging features of the carotid artery disease and carotid Doppler ultrasonographic

measurements, in which stent patency was controlled after the procedure, were collected from case follow-up forms and medical records.

Procedure

The treatment of acetylsalicylic acid (doses of 300 mg loading and 100 mg maintenance) and clopidogrel (doses of 600 mg loading and 75 mg maintenance) was routinely given to the patients before the procedure of carotid artery stenting. The procedure was performed with local anesthesia to the patients who were IV heparinized and had an activated clotting time (ACT) between 300 and 350. A 9F sheath was placed by entering the femoral artery with a percutaneous technique. With the support of 5F head hunter catheter and 0.035-inch hydrophilic guidewire (Terumo Corp Japan), the external carotid artery (ECA) was passed. After imaging ECA with opaque material, a proximal protection device (MoMA Invatec S.p.a Italy) was inserted with a 0.035-inch extra support guidewire through the 5F head hunter (Figure 1). Subsequently, the ECA occlusion balloon and then the common carotid balloon were inflated, and it was observed that there was no proximal blood flow with slow injection. Proximal MoMA balloons were deflated to reduce occlusion time after the insertion of the distal protection filter (Emboshield NAV6 Abbott Vascular USA) into the lesion (Figure 2). Stent implantation was performed using closed-cell Xact and Wall stents due to the high thrombus load of the lesions after pre-dilatation. The procedures were finalized by removing the distal filter and taking intracranial images (Figure 3). Femoral artery was closed with ProGlide and Angio-Seal closure devices.

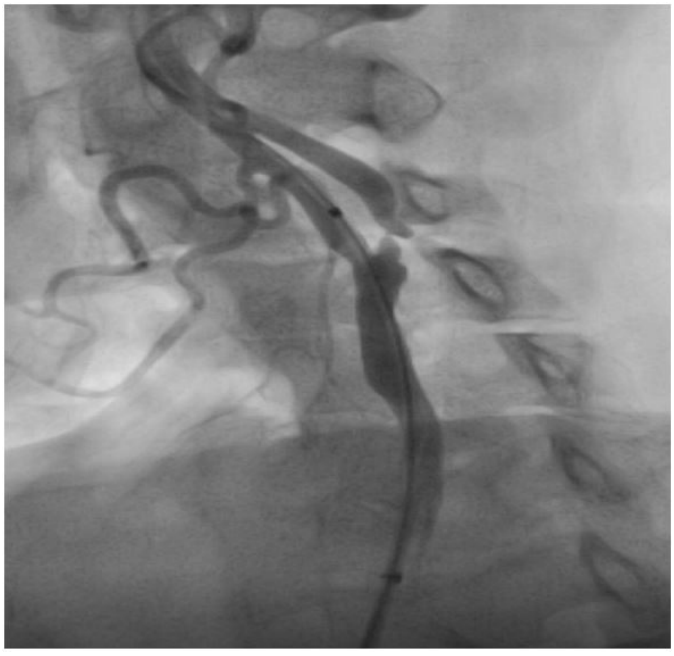

Figure 1. Placement of MoMa catheter

Clinical Characteristics

Baseline demographic characteristics of the patients are summarized in Table 1. When the co-morbidity and lesion characteristics were examined, it was seen that the patients were in the high-risk group in terms of thromboembolic complications.

Statistical Analysis

The baseline demographics, risk factors, procedural data, and angiographic measurements were obtained from case follow-up forms and angiographic images.

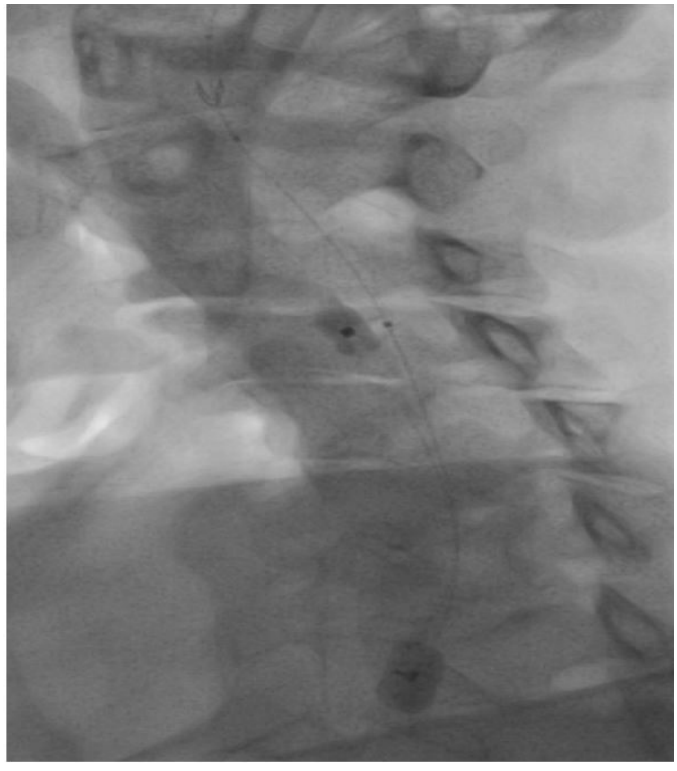

Figure 2. Placement of distal filters by inflating MoMa balloons

Data analysis was performed with the SPSS 18 program. A comparative analysis could not be performed since there was no control group. The Kolmogorov-Smirnov test was used to determine whether the variables were normally distributed. The mean ± standard deviation was used to evaluate the normal distribution of continuous variables. Variables that did not show normal distribution were expressed as median. In addition, the evaluation of categorical data was shown as percentage.

Results

The mean age of the patients was 76±7.1 years, and 13 of the patients were male. Baseline demographic characteristics of the patients are summarized in Table 1. Patients were at high risk for thromboembolic complications in terms of both comorbidities and plaque morphology. CAS was applied to the right internal carotid artery in 58.8% of the patients and to the left internal carotid artery in 41.1% of the patients. It was observed that carotid lesions had distal tortuosity and ulceration in 58.8% and were calcified in 41.1%. The characteristics of the lesions are summarized in Table 2. Stenting was performed successfully in all patients. No death was observed during the procedure, but contralateral major stroke was observed in one of the patients and transient ischemic attack was observed in two of the patients. Procedural adverse events are summarized in Table 3. Doppler USG was used in the diagnosis of restenosis since it was noninvasive and reproducible. Restenosis was assessed by examining the peak systolic velocity values. When the medical records were investigated retrospectively, it was observed that 13

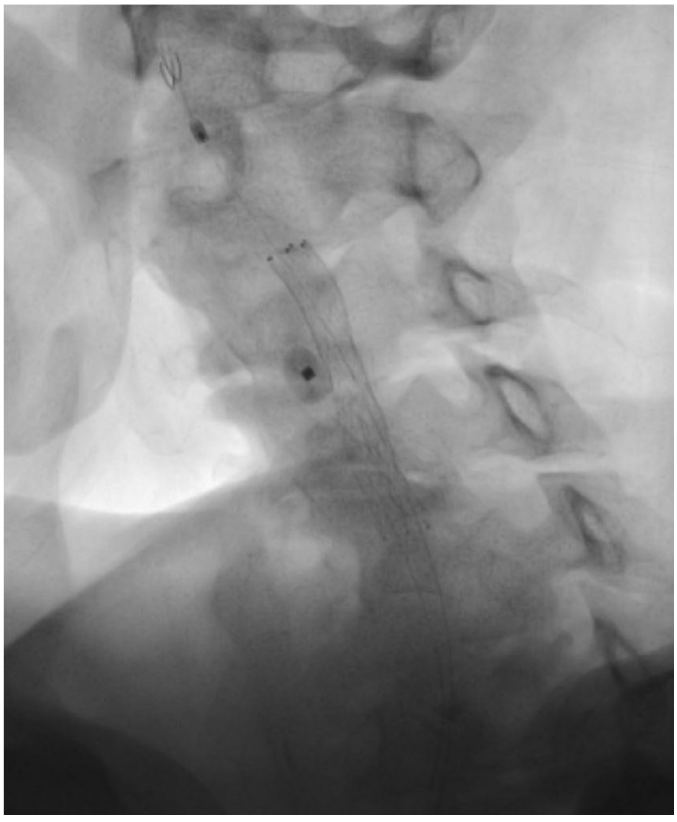

Figure 3. Placement of stent

Table 1. Basal characteristics of the patients

Demographic characteristics	n (%)
Age, years (mean ± SD)	76±7.1
Male gender	13 (76.5)
Hypertension	17 (100)
Diabetes mellitus	14 (82.3)
Dyslipidemia	15 (88.2)
Smoker	15 (88.2)
Peripheral artery disease	13 (76.5)
Chronic lung disease	11 (64.7)
Coronary artery disease	15 (88.2)
Symptom	17 (100)
Transient ischemic attack	13 (76.5)
Stroke	12 (70.6)
GFR (mL/min)	42

GFR: Glomerular filtration rate, SD: Standard deviation, n: Number

Table 2. Lesion characteristics

Lesion characteristics	n (%)
Target carotid artery	
Right	10 (58.8)
Left	7 (41.2)
Contralateral carotid artery occlusion	4 (23.5)
Degree of stenosis (mean ± SD)	81.6±9.7
Lesion length, mm (mean ± SD)	24±3.8
Calcification	7 (41.2)
Ulceration	10 (58.8)
Distal tortuosity	7 (41.2)
External carotid artery disease	2 (11.8)

SD: Standard deviation, n: Number

Table 3. Procedural adverse events

Adverse Events	n (%)
Contralateral major stroke	1 (5.8)
Ipsilateral minor stroke	0
Ipsilateral TIA	2 (11.8)
Amaurosis fugax	0
Myocardial infarction	0
Femoral hematoma	3 (17.6)
Death	0
Prolonged hypotension	2 (11.8)

TIA: Transient ischemic attack, n: Number

out of 17 patients had control carotid Doppler USG twice, 6 and 12 months after the procedure. All of the stents were still open in these patients.

Discussion

In this study, it was shown that the combined use of distal and proximal cerebral protection devices could be applied successfully with low complication rates in high-risk patients. Embolic stroke is the most feared complication of carotid artery stenting. Carotid artery stenting is performed with low complication rates in experienced centers. In the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study, the results of carotid stenting, which was performed with cerebral protection devices, were investigated in patients at high risk for carotid endarterectomy[6]. In the SAPPHIRE study, the rate of procedural stroke and death was 3.7% in the stent group and 5.3% in the endarterectomy group. However, the 3-year results of the same study were similar in both groups. In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) study, it was observed that carotid stenting was similar to carotid endarterectomy, but there was an increased risk of stroke with carotid stenting[7]. Previous studies have reported that the use of the distal filter alone caused increased ischemic complications due to the debris occurring during the procedure[8]. It has been reported that ischemic complications increase during carotid stenting, especially in tortuous lesions and lesions with lipid-rich necrotic nuclei, and/or in intra-plaque hemorrhages[9]. Diffusion MRI indicated that debris smaller than the pores of the filter could pass into the brain in patients who were intervened with distal stent filtration alone. In the Prevention of cerebral embolization by proximal balloon occlusion compared to filter protection during carotid artery stenting study (PROFI), post-procedure diffusion MRI was evaluated in patients with distal filters, and new lesions were detected in up to 87% of these patients[10]. By interrupting the antegrade flow with proximal cerebral protection devices, migration of debris (that may occur during the intervention) to the brain is prevented. However, interruption of antegrade flow may cause ischemic intolerance, especially in patients with bilateral lesions or contralateral total occlusion. Therefore, complete carotid angiography should be performed before the procedure to evaluate the collateral flow. In this way, after determining the flow in the contralateral carotid artery, vertebrobasilar artery and anterior-posterior communicating arteries, the embolism protection device to be used during the procedure should be selected. The procedure should be performed under general anesthesia and with close hemodynamic monitoring, especially in patients with suspected ischemic intolerance and in whom a proximal cerebral protection device will be used. In cases in whom double thromboembolism protection devices were used, in order to avoid ischemic intolerance, the common carotid balloon was inflated during the filter pass and the MoMa balloon was deflated after the filter was opened to protect the brain from ischemic intolerance. Confusion and slurring in speech were observed in only three patients during the procedure while the balloon was inflated, and full recovery was observed after the balloon was deflated.

Reports from the Carotid Stenting Trialists' Collaboration (CSTC) showed that increased stroke and death risk for individuals treated with CAS versus CEA in those aged 70 years or older, although the stroke and death risk was similar for the two procedures for those younger than 70 years old[11]. The majority of the patients included in our study were aged ≥70 years old. In the literature,

the frequencies of periprocedural events and death were reported to be increased after CAS in this age group, but no death after CAS was observed in our study. A decrease in the frequency of incidents was observed with the use of double protection device during the procedure.

Currently, two major stent categories are used in carotid artery stenting, open- and closed cell stents. Closed cell stents have tighter weaves so these stents are more rigid and may also cause arterial kink formation. Therefore, they are not suitable for use in tortuous vessels. On the other hand, open cell stents are more flexible and require less manipulation during CAS. So open cell stents are less risky in terms of embolism due to catheter manipulation. In addition, the distal filter is easier to collect after the procedure because of the stent flexibility. Restenosis rate and procedure-related complication rates were also found to be lower in open cell stents than in closed cell stents[12].

Choosing a carotid stent is important in patients with contralateral complete occlusion or bilateral severe stenosis, and in those who were evaluated to be at high risk based on imaging methods. The risk of thromboembolism is high during distal filtration with the use of open-cell stents, especially in patients with thrombosed lesions. Therefore, if there is a collateral blood flow in thrombosed lesions, it is appropriate to choose closed-cell stents, and to use a proximal cerebral protection device, which prevents antegrade flow. Closed-cell stents consist of cells that connect to each other at every point and have a better support for the vessel wall. However, the flexibility of closed-cell stents is lower due to the high number of connections. Therefore, it is difficult to use closed-cell stents in vessels with high tortuosity. For these reasons, the use of a double protective device with an open cell stent is considered appropriate in patients with high risk of embolism and especially in patients with tortuous anatomy.

Conclusion

As a consequence, double cerebral protection devices can be applied safely with high procedural success and low complication rates in patients with high thromboembolism risk. The safety of the procedure can be demonstrated by the use of highly sensitive imaging methods, such as diffusion MRI, in the detection of post-procedure thromboembolic complications. The small number of cases is a limitation of the present study and prevents the generalizability of the results. There is a need for further studies with large cohorts.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Ankara City Hospital with the number of E1-20-1501 on date 20.01.2021.

Informed Consent: Informed consents were obtained from the patients.

Peer-review: Externally peer-reviewed.

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Acute Myocarditis Mimicking ST-Elevation Myocardial Infarction in an 18-Year-Old Patient with Thyroiditis

Huseyin Ede[1], Shabir Ali Haider[1], Imad Awwad Ahmed[2], Haisam Hamdi Alsadi[1]

[1]Hamad Medical Corporation Heart Hospital, Department of Cardiology, Doha, Qatar
[2]Hamad Medical Corporation Heart Hospital, Department of Radiology, Doha, Qatar

Abstract

Acute myocarditis can manifest in a different clinical form ranging from subclinical disease to death. In these clinical presentations, acute myocarditis can easily be misdiagnosed as acute ST-elevation myocardial infarction. Therefore, its differential diagnosis is very crucial in the management. Acute thyroiditis may also have similar pathobiological causes as acute myocarditis but the concomitant occurrence is very rare. Here, we presented a case of acute myocarditis mimicking ST-segment elevation myocardial infarction in an 18-year-old patient with concomitant acute thyroiditis and initial normal inflammatory markers.

Keywords: Acute myocardial infarction, myocarditis, thyroiditis, echocardiography

Introduction

Acute myocarditis develops due to inflammation of cardiac muscle and it needs differential diagnosis[1]. Its clinical presentation varies from subclinical disease to heart failure, cardiogenic shock, and even death[2]. The symptoms such as fatigue, dyspnea, peripheral edema, and chest discomfort usually develop over weeks and months. However, typical acute-onset angina can also be observed in patients with acute myocarditis although not commonly. Additionally, it can sometimes mimic

Address for Correspondence: Huseyin Ede, Hamad Medical Corporation Heart Hospital, Department of Cardiology, Doha, Qatar
e-mail: huseyinede@gmail.com **ORCID:** orcid.org/0000-0003-1218-257X
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acute coronary syndrome with ST elevation myocardial infarction (ACS/STEMI).

Thyroiditis is commonly associated with viral and bacterial pathogens, autoimmune diseases, drugs, radiation, or trauma[3]. However, acute myocarditis with concomitant acute-onset thyroiditis with normal inflammatory markers at presentation is very rare in the literature. Here, we presented an 18-year-old male patient with ACS/STEMI-like acute myocarditis and thyroiditis without obviously elevated inflammatory biomarkers or preceding respiratory tract infection.

Case Report

An 18-year-old male patient without any significant past medical history was brought to Emergency Department due to a new-onset, retrosternal, pressure-type chest pain lasting for 3 hours, with hotline electrocardiography (ECG) finding showing 0.5 mm ST depression over V1 and aVR and 2 mm ST elevation over II, III, aVF (Figure 1a). On arrival in the emergency department (ED), the patient was free of chest pain with similar ST changes as the hotline ECG (Figure 1b). Physical examination showed blood pressure of 107/57 mmHg, heart rate of 111 bpm with oxygen saturation of 97% at room air. Chest and cardiac exams were unremarkable except for mild tachycardia.

Bedside point-of-care ultrasonography (POCUS) revealed normal left ventricular ejection fraction (LVEF) without regional wall motion abnormalities or pericardial effusion. An urgent detailed echocardiographic exam confirmed similar findings as those of POCUS (LVEF of 56%). Initially, the patient was managed conservatively with differential diagnoses of perimyocarditis and acute coronary syndrome.

In the laboratory findings, the white blood cell count was 9.2 10^3/µL, hemoglobin was 13.4 gr/dL, high-sensitivity troponin T levels were significantly elevated (1312 ng/L at admission, 1155 ng/L after three hours, and 2828 ng/L after 24 hours after the admission with normal renal function). Alanine transaminase and aspartate transaminase levels were 32 U/L and 113 U/L, respectively, with normal bilirubin level (14 µmol/L) (Table 1). The patient had total cholesterol level of 4.1 mmol/L, LDL of 2.7 mmol/L, triglyceride of 0.5 mmol/L and HDL of 1.2 mmol/L. Serum C-reactive protein (CRP) level was 2.6 mg/L, procalcitonin 0.02 ng/mL at admission.

The patient developed similar chest pain with more prominent ST elevation over II, III, aVF, V5, V6, V7, V9) (Figures 1c and d) 3 hours after the arrival in ED. The patient was promptly transferred to the cardiac catheter laboratory to rule out possible coronary artery-related acute coronary syndrome while he was having ongoing chest pain. The coronary angiogram showed normal epicardial coronary arteries without spasm or dissection (Figure 2). Acute myocarditis treatment was initiated with ibuprofen 400 mg tablet three times a day and colchicine 0.5 mg tablet twice a day along with metoprolol 12.5 mg twice a day. Cardiac magnetic resonance imaging (CMRI) was performed 48 hours after the admission. It showed high normal LV volumes with moderately impaired systolic function (LVEF 42%), basal-to-apical anterior, lateral, and inferior walls hypokinesia with corresponding myocardial edema, subepicardial early and delayed hyperenhancement (Figure 3). The diagnosis was confirmed accordingly. Subsequently, ibuprofen was changed to aspirin 600 mg tablet three times a day and lisinopril 2.5 mg daily was added to the treatment plan. At follow-up, the results of respiratory panel, tested via polymerase chain reaction (PCR) (including influenza virus, parainfluenza virus, adenovirus, coronavirus disease-2019 (COVID-19), MERS coronavirus, human bocavirus, human enterovirus, human rhinovirus, the respiratory syncytial virus, Bordetella pertussis, legionella pneumophila, and human metapneumovirus), were unremarkable in nasopharyngeal swab. Additionally, the results of antineutrophil cytoplasmic antibody and antinuclear antibody blood tests were negative.

Coincidentally, the patient was diagnosed with painless, overt hyperthyroidism (thyroid-stimulating hormone (TSH) of 0.03 mIU/L, FT4 of 35.2 pmol/L and

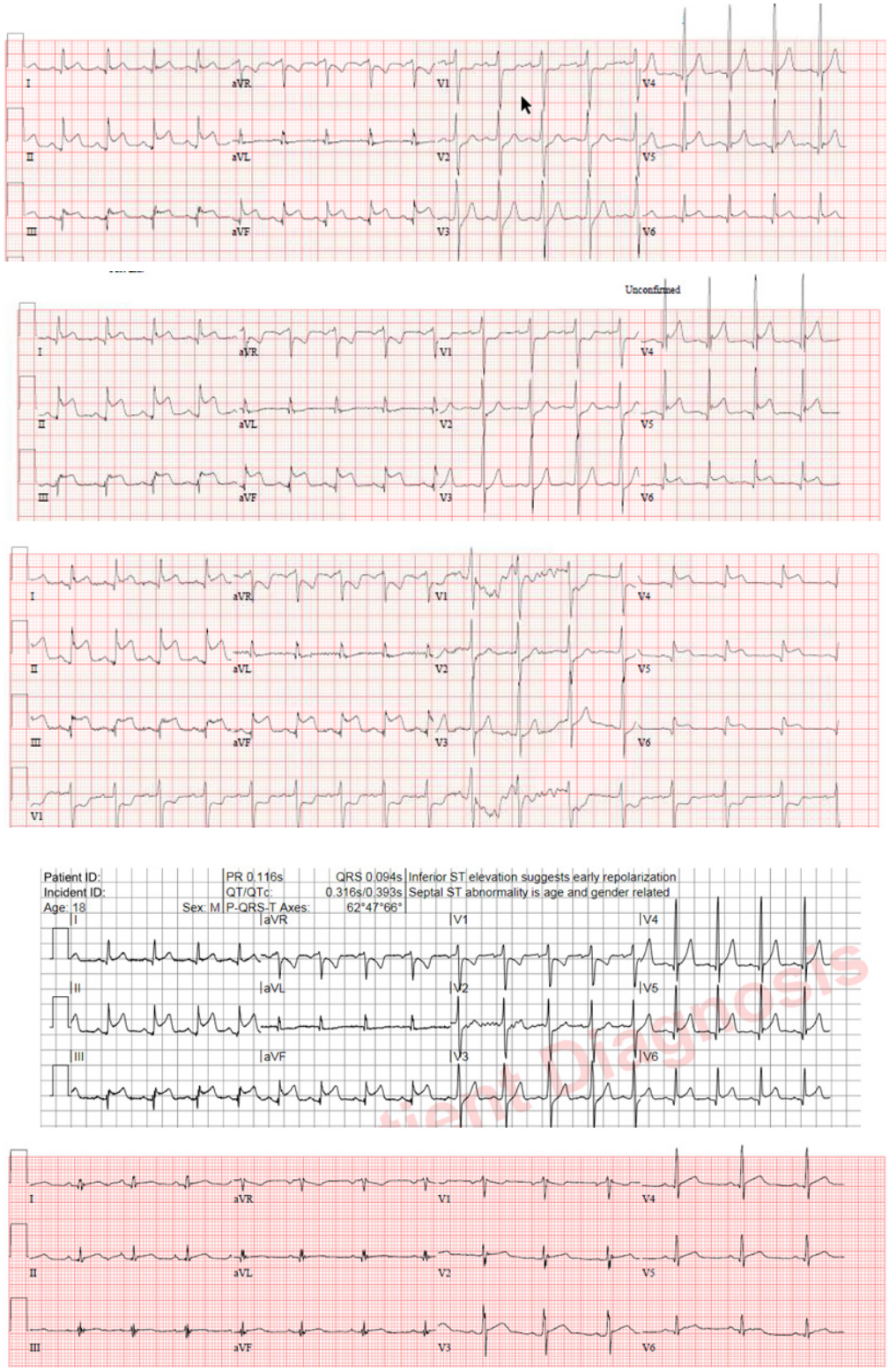

Figure 1a. Hotline electrocardiography (ECG) by the ambulance team; **1b)** ECG at arrival; **1c)** standard 12-lead ECG when chest pain developed 3 hours after the arrival; **1d)** ECG with posterior leads; V4, V5, and V6 stand for V7, V8, and V9 respectively; **1e)** 12-lead ECG at discharge in the 6th day.

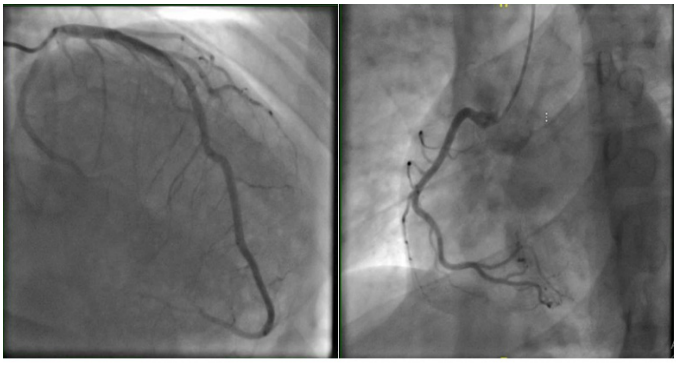

Figure 2. The coronary angiogram showed normal coronary artery

FT3 of 33.9 pmol/L at the admission) with the absence of anti-thyroid peroxidase or TSH receptor antibodies. The thyroid function tests improved within the following days without starting any anti-thyroid agent. (TSH of 0.04 mIU/L, FT4 of 13.3 pmol/L at day 5 after the admission) (Table 1). Both lobes of the thyroid gland and isthmus region were normal in size and shape with normal parenchymal echotexture and no focal lesions in thyroid ultrasonography. Additionally, few cervical lymph nodes were detected bilaterally, in the right side measuring around 12x4 mm and in the left side measuring around

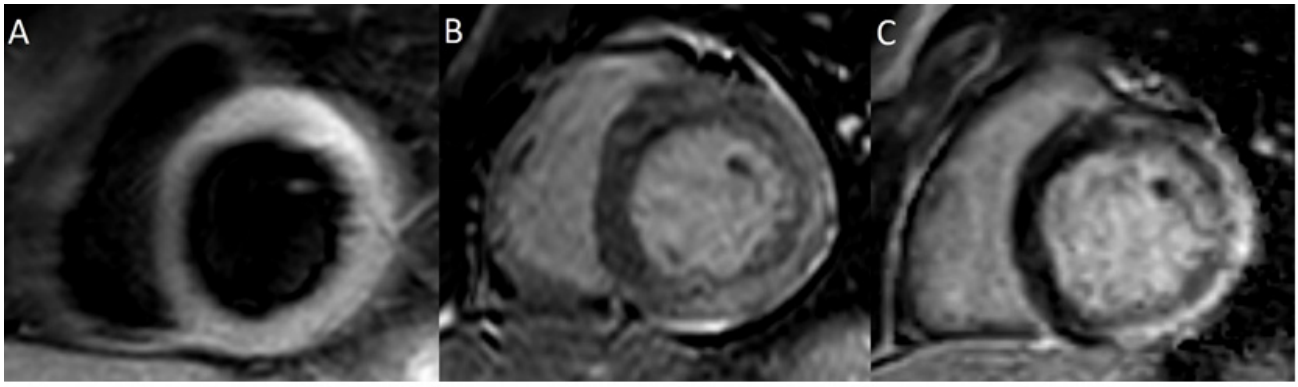

Figure 3. Cardiac magnetic resonance imaging showed the changes in consistent with acute myocarditis

Table 1. Laboratory and clinical findings of the patient during the follow-up in the hospital

	At arrival	3 hours after the arrival	6 hours after the arrival	24 hours after the arrival	2nd day	3rd day	4th day	5th day	6th day
WBC (4.0-10.0 10^3/μL)	9.2			7.3	8.6				
hs-Trop T (3-15 ng/L)	1312	1115	1950	2828			4358	3054	1351
TSH (0.50-4.30 mIU/L)	0.03					0.01		0.04	
FT3 (3.7-6.4 pmol/L)	33.9					4.0			
FT4 (12.9-20.6 pmol/L)	35.2					18.2		13.3	
ALT (0-41 U/L)	32			52	50	33		32	
AST (0-40 U/L)	113			293	194	49		19	
Heart rate (bpm)	111	99	95	100	103	86	70	79	81

WBC: White blood cell count, hs-Trop T: High-sensitivity troponin T, TSH: Thyroid stimulating hormone, ALT: Alanine transaminase, AST: Aspartate transaminase, bpm: Beats per minute

16x4 mm in size. Thus, the findings were consistent with acute thyroiditis.

The patient was discharged in stable condition with aspirin, colchicine, lisinopril 2.5 mg daily, and metoprolol 25 mg twice a day and with evolving ECG at day 6 (Figure 1e).

Discussion

In this case report, we presented concomitant acute myocarditis and acute thyroiditis without obvious inflammatory status, mimicking acute coronary syndrome in an 18-year-old male patient. We aimed to share our experience in diagnosis, treatment, and follow-up of such a young patient.

Acute myocarditis can mimic acute coronary syndrome[4]. As in this case, it is very easy to mix the diagnosis with acute myocardial infarction, considering his initial manifestations such as dynamic ECG changes with recurrent, typical, burning-like retrosternal angina, and normal CRP in absence of PR segment deviation, fever or recent upper respiratory infection.

Considering the initial ECG changes (ST-segment elevation without PR deviation), it can be clearly stated that the patient was at the beginning stage of acute myocarditis. As per the literature, transient ST elevation is often seen and disappears within 48 hours in 74% of all patients manifested with initial ST-segment elevation[5]. In our case, ST elevation at the admission almost disappeared on the day 6th.

It is very rare to develop ACS/STEMI at young age in the absence of risk factors. In general, less than 10% of patients with myocardial infarction are younger than 40 years old[6]. In the literature, ACS/STEMI at a young age without prominent risk factors (21 and 27 years old patients respectively) were reported previously[7]. Our case was 18 years old, without risk factors. with the recurrence of chest pain, coronary angiography (CAG) was performed and showed normal coronaries. This case was not an example of myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) since CMRI revealed changes that were consistent with myocarditis.

Another interesting finding of the patient was mild sinus tachycardia at the admission and at the following hours in the absence of any chest pain or heart failure symptoms although it is commonly observed in acute myocarditis, especially as a warning sign of heart failure and shock. Interestingly, the patient had concomitant overt hyperthyroidism due to acute thyroiditis along with acute myocarditis. Thyroid functions returned to near normal at day 5 without any intervention. Concomitant myocarditis and thyroiditis may develop in autoimmune diseases or drug exposure in animal models[7]; but are not described in humans. Autoimmune biomarkers were negative in our patient. Viral pathogens are the most common reason for acute myocarditis or thyroiditis[1,8]; but it is very difficult to isolate the causative agent most of the times. In our case, we also could not isolate any viral pathogen.

In conclusion, acute myocarditis and acute thyroiditis can be observed in the same patient. Thyroiditis-related hyperthyroidism should be suspected in an unexplained tachycardia at presentation. Myocarditis should be considered in the differential diagnosis of acute angina at a young age, especially in the absence of obvious risk factors regardless of initial inflammatory marker levels.

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Ethical and institutional approvals were obtained (MRC-04-21-656, dated on 06/09/2021).

Ethics

Informed Consent: It was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.E., S.A.H., I.A.A., H.H.A., Concept: H.E., S.A.H., I.A.A., H.H.A., Design: H.E., S.A.H., I.A.A., H.H.A., Data Collection and/or Processing: H.E., I.A.A., Analysis and/or Interpretation: H.E., S.A.H., H.H.A., Literature Search: H.E., S.A.H., I.A.A., H.H.A., Writing: H.E., S.A.H., I.A.A., H.H.A.

Conflict of Interest: The authors declare that they have no conflict of interest.

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May a Relationship Occur Between Peripartum Cardiomyopathy and Restrictive Cardiomyopathy?

Hatice Taşkan, Serkan Asil, Ender Murat, Selen Eşki, Hasan Kutsi Kabul

Gülhane Training and Research Hospital, Department of Cardiology, Ankara, Turkey

Abstract

Peripartum cardiomyopathy is a rare type of systolic heart failure at the end of pregnancy or in the months after birth, affecting young women. Restrictive cardiomyopathy is a rare form of predominantly diastolic heart failure and is difficult to diagnose. To date, there has been no case report showing the relationship between restrictive cardiomyopathy and peripartum cardiomyopathy. In this case report, a 35-year-old female patient who presented with heart failure symptoms and was diagnosed with restrictive cardiomyopathy and history of peripartum cardiomyopathy will be presented.

Keywords: Peripartum cardiomyopathy, restrictive cardiomyopathy, 'dip and plateau pattern' or 'square root sign'

Introduction

Restrictive cardiomyopathy (RCMP) is an uncommon category of the disease characterized by increased ventricular stiffness with poor prognosis and no effective treatment in the presence of normal diastolic volume and ventricular wall thickness[1,2]. Peripartum cardiomyopathy (PPCM) is a form of systolic heart failure that affects young women at the end of pregnancy or in the months after birth[3]. To date, there has been no publication or case report on the relationship between these two clinical conditions. We will describe a novel case of RCMP with a history of PPCM that was 7 years ago.

Address for Correspondence: Serkan Asil, Gülhane Training and Research Hospital, Department of Cardiology, Ankara, Turkey
e-mail: dr_serkanasil@hotmail.com **ORCID:** orcid.org/0000-0002-6782-4237
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Case Report

A 35-year-old female was admitted to our clinic with the symptoms of leg swelling and shortness of breath. The patient's physical examination revealed rales in two lung bases and pretibial oedema, electrocardiogram showed incomplete right bundle branch block and loss of R progression in anterior leads. Complete blood count, kidney, liver function tests, and cardiac enzymes were found to be normal, PRO-BNP was 1185 mg/dL.

The patient's medical history had PPCM. According to the patient's medical records of seven years ago, we obtained that left ventricular function decreased globally (EF=45%) in the transthoracic echocardiography and diastolic dysfunction was normal. The patient had been treated with ACE inhibitor and beta-blocker for 2 years after the diagnosis of PPCM. At the end of the 2nd year, due to her clinical complete recovery, her medical treatment had been discontinued, and her follow-up echocardiograms showed normal systolic functions.

Transthoracic echocardiography performed on the patient's application to us showed that EF 45%-50% decreased left ventricular systolic functions in the mid-range, dilated left and right atria, right ventricular systolic function was suppressed and increased in size. Doppler echocardiography showed increased early diastolic filling compared to atrial filling and increased E/A and E/e´ ratio (Figure 1). It was determined that there was moderate

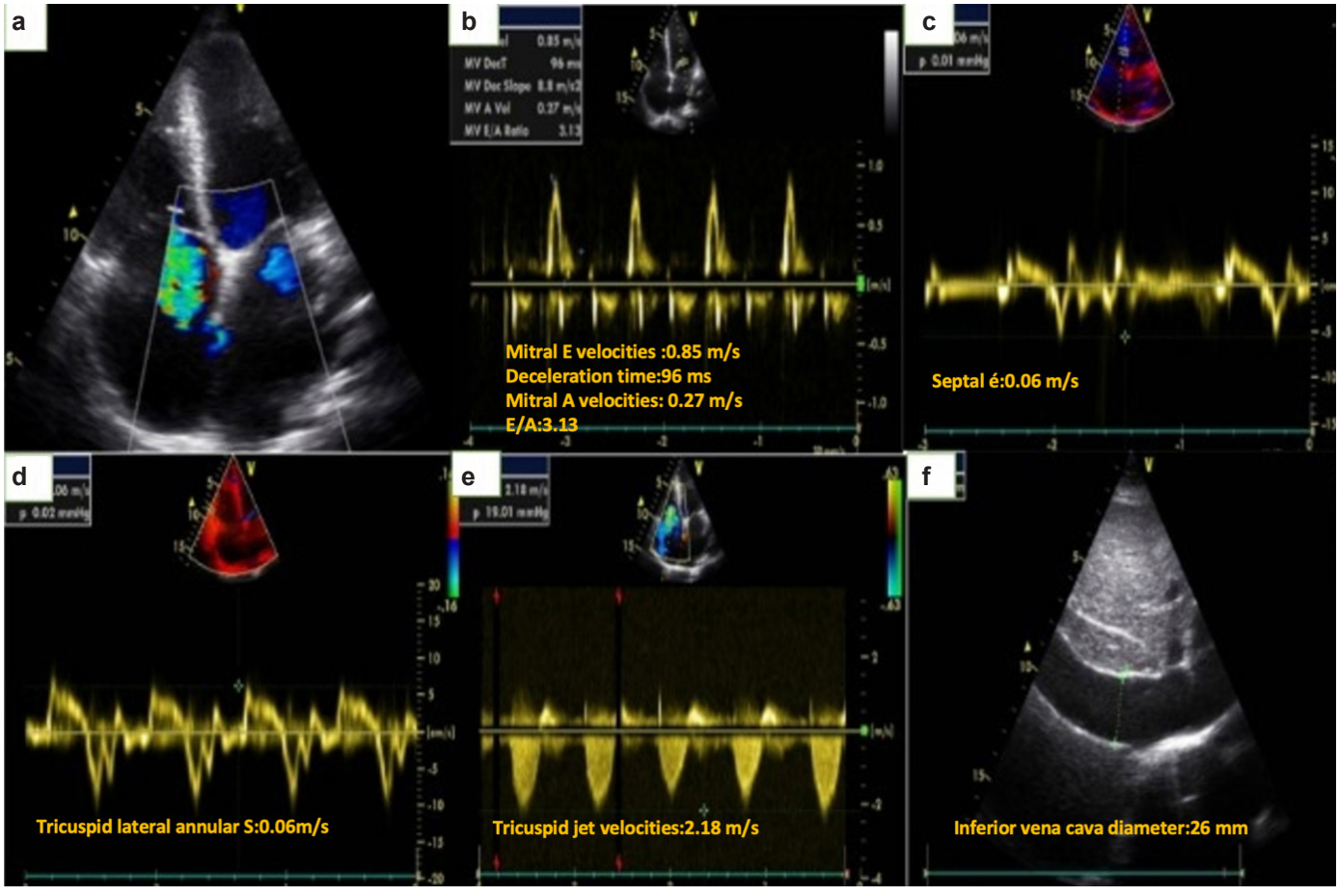

Figure 1. a) Echocardiography reveals biatrial enlargement. **b)** Doppler echocardiography shows increased early diastolic filling to the atrial filling ratio. **c)** Doppler echocardiography myocardial velocities of the basal septal wall. **d)** Tricuspid lateral annular S': 0.06 m/s. **e)** Severe tricuspid regurgitation, and tricuspid jet velocity: 2.18 m/s **f)**, inferior vena cava pleathore and measured diameter 26 mm

mitral regurgitation, severe tricuspid regurgitation, and systolic pulmonary artery pressure of 40 mmHg. Tricuspid valve coaptation was impaired, passage from left to right through the patent foramen ovale (PFO) tunnel was observed (Figure 1). After that, we performed Cardiac magnetic resonance imaging (MRI) for differential diagnosis. Both ventricular functions decreased globally in cardiac MRI (Left ventricular ejection fraction was 36%, right ventricular ejection fraction was 21%). Late contrast images showed patchy mid-myocardial subepicardial areas of late enhancement in the left ventricular basis and mid-myocardial-subepicardial levels on all walls. No calcification, thickening or adhesion of the heart was detected in the pericardium (Figure 2).

Considering these findings, cardiac catheterization was performed on the patient with a pre-diagnosis of RCMP. Coronary arteries were found to be normal in coronary angiography. Left and right catheterization revealed that left ventricular pressure was 125/22 mmHg, aortic pressure was 125/72/90 mmHg, right atrium pressure was 22 mmHg, right ventricular pressure was 40/22 mmHg, and mean pulmonary artery pressure was 28 mmHg. In the examination of the pressure records, it was observed that the diastolic pressure of both ventricles increased, and the difference between the diastolic pressure of the left and right ventricle was less than 5 mmHg. 'Dip and plateau pattern' or 'square root sign' was detected, and the diagnosis of RCMP was confirmed (Figure 2). The patient was evaluated as RCMP, and her medical treatment was arranged. In the follow-up, the implantable defibrillator was implanted in the patient who had progressive heart failure and non-sustained ventricular tachycardia attacks despite maximal medical therapy and was referred for heart transplantation list. After 10 months of follow-up, the patient, who was hospitalized with advanced heart failure and appropriate ICD shocks, died on the 3rd day of his admission.

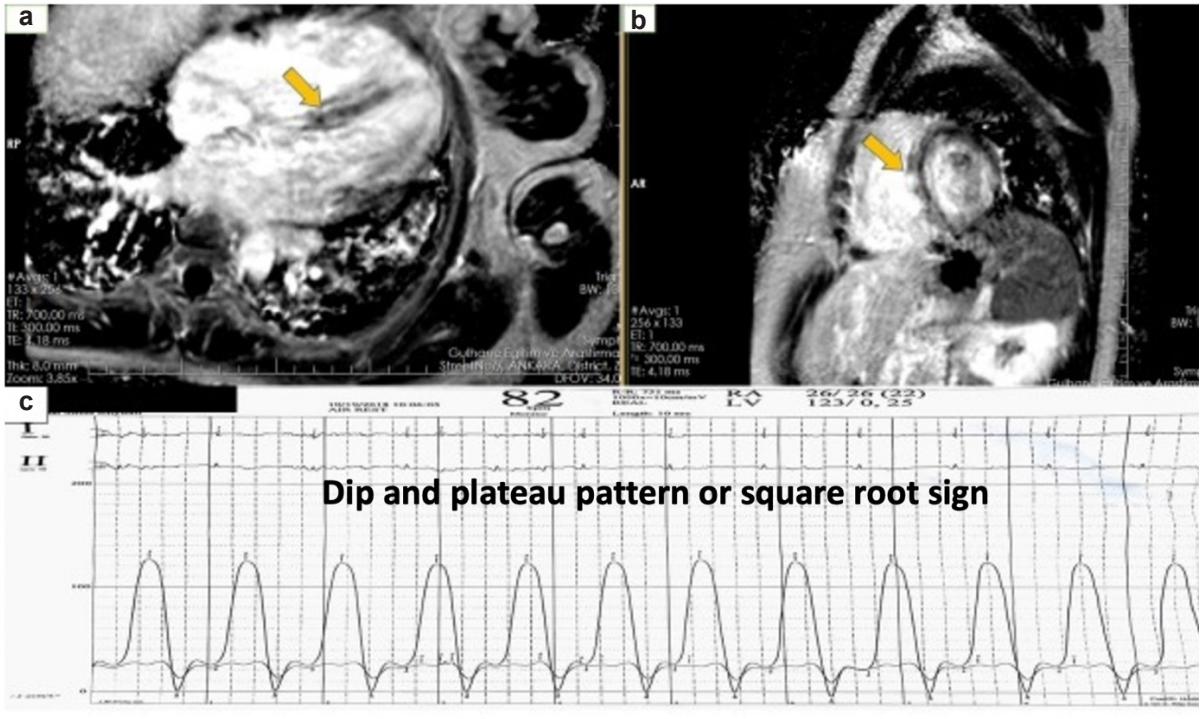

Figure 2. a, b) Cardiac magnetic resonance image of late enhancement in the left ventricular basis and midmyocardial-subepicardial levels on all walls. **c)** Equalization of left and right ventricular end-diastolic pressure and characteristic 'Dip and plateau pattern' or 'square root sign'

Discussion

In this case report, it was emphasized that two very rare types of heart failure occurred in the same patient at different times. Although there were no clear data to reveal the relationship between PPCM and RCMP, this situation has created some suspicions. We wanted to share this case to draw attention that in the late period, PPCM may be involved in the pathogenesis of RCMP, and to define future cases.

RCMP can result from a combination of hereditary or acquired predispositions and diseases, which can be narrowly categorized as infiltrative, storage, non-infiltrative, and endomyocardial[4]. Certain echocardiographic and clinic signs and symptoms could raise the suspicion of specific diagnoses such as amyloidosis and desmopathies[5]. However, there were no such signs and symptoms suggestive of diagnoses in our patient. Increased creatine kinase is seen in desmopathies, and increased proteinuria is seen in amyloidosis[5]. In our case, CPK was normal and the patient had no proteinuria, no thickening of the left ventricular wall. Based on these results, we diagnosed our patient with idiopathic RCMP.

After we suspected that PPCM, which the patient had experienced during her pregnancy 7 years ago, might present with RCMP in the late period, we searched the patient's medical records and literature. However, we could not find any evidence of RCMP in our patient's medical record. Also, in the literature review, we could not find any evidence on that PPCM causes RCMP. There have been very few cases of pregnant RCMP patients [6,7]. So, indicating the presence of PPCM in the patient's history, we could not term the case as idiopathic RCMP. However, we think that the relationship between PPCM and RCMP in this patient will help to define future cases.

Patients with RCMP typically experience serious signs of heart failure within a brief span of time and, unless they undergo a cardiac transplant, most die within a few years after diagnosis[8]. In our case, the patient had an asymptomatic period of about 5 years after the diagnosis of peripartum cardiomyopathy, during which she did not receive any treatment.

In conclusion, should PCMP and RCMP be considered separate events in this case, or could PCMP have caused RCMP? Since both diseases are rare, they are much less likely to be seen in the same patient. This is a novel case of RCMP occurring seven years after PCMP. Although the underlying mechanism is not known, a relationship with PCMP is suspected.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., Concept: S.A., H.K.K., Design: S.A., H.K.K., Data Collection and/or Processing: H.T., E.M., S.E., Literature Search: S.A., E.M., S.E., Writing: S.A., H.T.

Conflict of Interest: The authors declare that they have no conflict of interest.

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