

Endovascular treatment of subclavian stenosis – single center experience

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ABSTRACT:

Introduction: Subclavian artery stenosis is a potential cause of serious morbidity, endangering the upper extremities, brain and the heart. It is a relatively rare form of peripheral arterial disease, usually present in patients who already suffer from peripheral arterial disease on other vessels, most often lower extremity arteries. Atherosclerosis is considered to be the primary underlying cause. The current treatment of choice is endovascular approach which combines percutaneous transluminal angioplasty and stenting as its noninvasive nature yields faster recovery and less complications.

Aim: The aim of this study was to examine the characteristics of subclavian atherosclerotic lesions in patients who underwent endovascular procedure and their relationship with known risk factors. Additional aim was to assess clinical and procedure characteristics of patients and compare them with similar experiences from other centers.

Patients and methods: We conducted a retrospective single center review of patients treated with endovascular procedure for SA stenosis and/or occlusion. A total of 53 patients were detected. Three patients were excluded due to the arteritis origin of the stenosis, leaving 50 patients suitable for analysis. Participants' characteristics were analyzed using descriptive statistics. Normal distribution was assessed using Shapiro-Wilk test. Categorical variables were analyzed using the Chi-square test. Univariate logistic regression was used to calculate unadjusted odds ratios of factors associated with level of stenosis.

Results: The mean age at the time of the first intervention was 62±8 years. All except 8 patients were symptomatic. The most common symptoms were paresthesia (32%), vertigo (30%), muscle fatigue (24%) and rest pain (22%). 58% of patients presented with Subclavian steal syndrome. The most common comorbidities and risk factors present in selected patients were hypertension 76%, smoking 60%, hyperlipidemia 60% and coronary artery disease 22%. A total of 50 lesions were treated with 59 endovascular procedures, 9 reinterventions among them. Technical success was achieved in 85% of procedures. After univariate analysis 3 items were detected suitable for multivariate logistic regression. The multivariate regression model was statistically significant $\chi^2(4, N = 50) = 17.94, p < 0.01$, explaining 42.7% of variance (Nagelkerke $R^2 = .427$). Female gender ($p < 0.05$), hypertension ($p < 0.05$) and smoking status ($p < 0.05$) were independently associated with occlusion. Women had 7.7 times the odds of developing occlusion compared to males. Moreover, patients with a history of hypertension were 5.1 times more likely to develop occlusion. Smoking was associated with 7.8 higher chances to develop occlusion. The results of multivariate analysis are of limited significance due to the small sample size.

Conclusion: Comparing this review with other similar studies, most of the clinical and demographic indicators were inconspicuous. Technical success was achieved in 85% of the procedures in our center, whereas in other studies it was markedly higher, ranging from 93% to 98%. Female gender was identified as an additional independent risk factor, although the relevant literature indicates male gender as the risk factor. Although hyperlipidemia is a known risk factor for atherosclerotic stenosis, it did not reach statistical significance in univariate analysis. This research provided a much needed insight into the characteristics of patients and effectiveness of interventions undertaken in our center.

KEYWORDS: subclavian stenosis, subclavian artery, occlusion, endovascular intervention, hypertension, gender, smoking, hyperlipidemia, stenting, angioplasty

SAŽETAK:

ENDOVASKULARNO LIJEČENJE STENOZE POTKLJUČNE ARTERIJE – ISKUSTVO JEDNOG CENTRA

Uvod: Stenoza potključne arterije je potencijalni uzrok ozbiljnog oboljenja koje može ugrožavati gornje ekstremitete, mozak i srce. Ona predstavlja relativno rijedak oblik periferne arterijske bolesti i obično je prisutna u bolesnika koji već imaju zahvaćene druge žile, najčešće na donjim ekstremitetima. Ateroskleroza se smatra glavnim uzrokom ove bolesti. Današnja metoda izbora u liječenju kombinira perkutanu transluminalnu angioplastiku sa stentiranjem koje zbog svojih neinvazivnih svojstava polučuju brži oporavak s manje komplikacija.

Cilj: Cilj ovog istraživanja je proučiti karakteristike aterosklerotskih lezija u pacijenata koji su imali endovaskularni zahvat te njihov odnos s poznatim čimbenicima rizika. Dodatni cilj bio je procijeniti karakteristike samih zahvata i usporediti ih sa sličnim istraživanjima iz drugih centara.

Ispitanici i metode: Proveli smo retrospektivno unicentrično istraživanje pacijenata liječenih endovaskularnim zahvatima zbog stenoze i/ili okluzije potključne arterije. Od 53 pacijenta troje je isključeno uslijed arteritisa, ostavivši ukupno 50 pacijenata pogodnih za daljnju analizu. Karakteristike pacijenata analizirane su pomoću deskriptivne statistike. Normalna distribucija procijenjena je koristeći Shapiro-Wilk test. Kategorijske varijable analizirane su pomoću Hi-kvadrat testa. Univarijatna logistička regresija korištena je za računanje neprilagođenih omjera šansi faktora povezanih sa stupnjem stenoze.

Rezultati: Srednja dob prilikom prve intervencije bila je 62±8 godina. Samo 8 pacijenata je bilo asimptomatsko. Najčešći simptomi bili su parestezije (32%), vrtoglavica (30%), mišićni umor (24%) i bol u mirovanju (22%). 58% pacijenata imalo je Subclavian steal sindrom. Najčešći komorbiditeti i čimbenici rizika bili su hipertenzija 76%, pušenje 60%, hiperlipidemija 60% te koronarna arterijska bolest 22%. Ukupno 50 lezija liječeno je u 59 endovaskularnih postupaka, među njima 9 reintervencija. Tehnički uspjeh postignut je u 85% slučajeva. Nakon univarijatne analize 3 faktora su se pokazala pogodnima za multivarijatnu logističku regresiju. Multivarijatni regresijski model pokazao je statističku značajnost $\chi^2(4, N = 50) = 17.94, p < 0.01$, objašnjavajući 42.7% varijance (Nagelkerke $R^2 = .427$). Ženski spol ($p < 0.05$), hipertenzija ($p < 0.05$) i pušački status ($p < 0.05$) bili su neovisno povezani s okluzijom. Žene su imale 7.7 puta veće šanse za razvoj okluzije u usporedbi s muškarcima. Pacijenti s hipertenzijom u anamnezi imali su 5.1 puta veću vjerojatnost za razvoj okluzije. Pušenje je u 7.8 puta češće uzrokovalo okluziju subklavije. Rezultate multivarijatne analize imaju ograničenu vrijednost zbog malog broja ispitanika.

Zaključak: Uspoređujući ovaj pregled sa sličnim istraživanjima u drugim centrima većina demografskih i kliničkih pokazatelja nisu pokazivali značajne razlike. Tehnički uspjeh u našem centru postignut je u 85% zahvata, dok je u drugim studijama iznosio između 93% i 98%. Ženski spol identificiran je kao nezavisni rizični čimbenik premda se u literaturi muški spol navodi kao rizičan. Iako se hiperlipidemija navodi kao poznati rizični čimbenik za razvoj ateroskleroze, nije pokazala statističku značajnost u univarijatnoj analizi. Ovo istraživanje omogućilo nam je dublji uvid u karakteristike pacijenata liječenih u našem centru te pokazalo na kojim poljima postoji mjesta za napredak.

KLJUČNE RIJEČI: stenoza subklavije, potključna arterija, okluzija, endovaskularne intervencije, hipertenzija, spol, pušenje, hiperlipidemija, stentiranje, angioplastika

INTRODUCTION

Peripheral arterial disease (PAD) is a condition characterized by narrowing of the arteries which do not supply the brain and heart (peripheral arteries). Atherosclerosis is considered to be the primary underlying cause of PAD. Risk factors such as hypertension, hyperlipidemia, diabetes and tobacco abuse promote the formation of atherosclerotic lesions. Subclavian artery (SA) stenosis is a relatively rare form of PAD, usually present in patients who already suffer from PAD on other vessels, most often lower extremity arteries. Other causes and conditions associated with SA stenosis include various forms of arteritis, thoracic outlet syndrome, fibromuscular dysplasia, and neurofibromatosis^{1,2}. The prevalence of subclavian stenosis in general population is around 2%. The prevalence is markedly higher in patients with PAD, with estimates ranging from 11.5% to 19%. In patients without PAD the prevalence of subclavian stenosis is 1.5%. It is 4.3% in patients with hypertension, 4.3% in patients with a history of smoking and 7.6% in patients with cerebrovascular disease^{1,2,3,4}. This condition is usually asymptomatic due to the slow progression of atherosclerotic plaques and the abundant collateral circulation associated with the circle of Willis⁵. The symptoms in symptomatic patients include claudication, muscle fatigue and rest pain. They appear sooner and are more prominent if other vessels are affected. In the case of a severe stenosis proximal to the vertebral artery (VA) the distal SA is supplied by blood flowing reverse from VA, a condition known as subclavia steal syndrome (SSS). It may be categorized as complete (with a reverse flow in VA during the entire cardiac cycle) or partial (with a reverse flow only during systole)⁶. SSS may result in vertebrobasilar insufficiency, manifesting symptoms as vertigo, syncope, headache, diplopia, blurred vision, dysarthria, tinnitus etc.^{5,7,8,9}. The diagnosis of SA stenosis is established by detecting different systolic blood pressure between the two arms (difference greater than 15 mmHg) and by duplex ultrasound which can estimate the grade of stenosis. The exact dimensions of stenosis are determined by computed tomography (CT) angiography and digital subtraction angiography (DSA). Further diagnostic procedures may include magnetic resonance imaging (MRI) with or without angiography^{7,10}. Treatment of SA stenosis is usually reserved for symptomatic patients and includes open surgery and endovascular approach with percutaneous transluminal angioplasty (PTA) and/or stenting. The current treatment of choice is endovascular approach which combines PTA and stenting as its noninvasive nature yields faster recovery and less complications¹⁰. The aim of this study was to examine the characteristics of SA atherosclerotic lesions in patients who underwent endovascular procedure and their relationship with known risk factors. Additional aim was to assess clinical and procedure characteristics of patients and compare them with similar experiences from other centers.

PATIENTS AND METHODS

We conducted a retrospective single center review of patients treated with endovascular procedure for SA stenosis and/or occlusion. All patients diagnosed and treated at the Department of Radiology of University Hospital Centre Zagreb, Croatia from January 2010 to December 2020 were included. A computer search using Radiologic Informatic System (RIS) database in our center was performed to identify the patients and obtain clinical and treatment details. Inclusion criteria included the patients who underwent endovascular procedures due to atherosclerotic stenosis and/or occlusion of SA. A total of 53 patients were detected. Three patients were excluded due to the arteritis origin of the stenosis, leaving 50 patients suitable for analysis.

STATISTICAL ANALYSES

Participants' characteristics were analyzed using descriptive statistics. Normal distribution was assessed using Shapiro-Wilk test. Categorical variables were analyzed using the Chi-square test. Univariate logistic regression was used to calculate unadjusted odds ratios of factors associated with level of stenosis. Factors with $P < .10$ on univariate analysis were included in multivariate analyses. Factors with $P < .05$ on multivariate analysis were considered significant. All tests were 2-tailed. Data analysis was performed with SPSS Version 20.

RESULTS

Among the 50 studied patients there was equal number of women and men. The mean age at the time of the first intervention was 62 ± 8 years. All except 8 patients were symptomatic. In asymptomatic patients endovascular procedure was undertaken prior to ipsilateral carotid endarterectomy. The most common symptoms were paresthesia (32%), vertigo (30%), muscle fatigue (24%) and rest pain (22%). 58% of patients presented with Subclavian steal syndrome. Only two patients developed critical limb ischemia.

The most common comorbidities and risk factors present in selected patients were hypertension 76%, smoking 60%, hyperlipidemia 60% and coronary artery disease 22%. (Table 1) Two patients suffered from renal insufficiency and two other from systemic lupus. Mean number of comorbidities per patient was 4.4.

Table 1. Comorbidities and risk factors in 50 patients who underwent endovascular treatment for SA stenosis and/or occlusion

Comorbidity or risk factor	Number of patients	%
Hypertension	38	76
Smoking	30	60
Hyperlipidemia	30	60
Coronary arterial disease	11	22
Endovascular procedure on any other vessel	10	20
Diabetes	10	20
Internal carotid artery stenosis	8	16
Stroke	8	16
Neoplasm	8	16

A total of 50 SA lesions were detected, 37 stenoses, of which 23 subocclusive, and 13 occlusions. Of those, 39 were on the left and 11 on the right. Mean length of lesions was 21 ± 11 mm. Only 6 lesions were 3 to 5 cm long. Most lesions were situated in the prevertebral segment of SA, only 4 were in distal segments. Mean grade of stenosis, without subocclusion, was 73% (IQ 60-80%). With subocclusion and occlusion mean grade of stenosis was $92 \pm 13\%$.

The management of patients included clinical examination coupled with bilateral arm pressure measurement. 28 patients were further evaluated using CT angiography. DSA was performed in all the patients in the same act as intervention.

The lesions were treated with 59 endovascular procedures, 9 reinterventions among them. Six patients had an in-stent stenosis which warranted reintervention. One patient had 4 interventions from 2016 to 2018. Right transfemoral approach was the most frequently used (62%), followed by left brachial approach (17%). PTA with stenting (primary stenting) was performed in 43 procedures, using 39 balloon-expandable stents and 4 self-expanding ones. PTA alone was done in 12 patients and the procedure was halted after just DSA in 4 cases due to impassable calcifications. Six in-stent stenoses were detected and two stent-in-stent interventions were carried out.

Mean diameter of the stents was 7.7 ± 1.3 mm, and mean stent length was 26.85 ± 13 mm.

Table 3. Multivariable logistic regression, $\chi^2 = 17.94$, *R square* = 42.7%.

		Variables in the Equation						95% C.I.for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step	Female gender	2,040	,825	6,119	1	,013	7,692	1,528	38,734
	Smoking	2,057	,822	6,254	1	,012	7,821	1,560	39,207
	Hypertension	1,636	,897	3,329	1	,068	5,134	,886	29,766
	Constant	-2,248	1,024	4,819	1	,028	,106		

Technical success was achieved in 85% of procedures. In 9 patients it was impossible to place the stent and/or perform PTA due to the calcified plaque which proved impassable for the guiding wire. No embolic complications were encountered and only 10 local complications were detected: 4 femoral hematomas, 4 brachial hematomas, 1 cubital hematoma and 1 SA dissection.

The fact that the majority of patients from this study weren't followed in our institution made it impossible to obtain data concerning follow up and to estimate the mid and long-term patency. For the purpose of the analysis of correlation of risk factors and severity of stenoses, North American Symptomatic Carotid Endarterectomy Trial (NASCET) method for calculating the grade of stenosis was used. Additionally, subocclusive stenoses were numerically categorized as 99% stenoses and occlusions as 100%^{2,11,12}. In logistic regression model subocclusive stenosis and complete occlusions were analyzed as a single category of dependent variable.

After univariate analysis 3 items were detected suitable for multivariate logistic regression (Table 2).

The multivariate regression model (Table 3) was statistically significant $\chi^2 (4, N = 50) = 17.94$, $p < 0.01$, explaining 42.7% of variance (Nagelkerke $R^2 = .427$). Female gender ($p < 0.05$), hypertension ($p < 0.05$) and smoking status ($p < 0.05$) were independently associated with occlusion. Women had 7.7 times the odds of developing occlusion compared to males. Moreover, patients with history of hypertension were 5.1 times more likely to develop occlusion. Smoking was associated with 7.8 higher chances to develop occlusion. The results of multivariate analysis should be interpreted with caution due to the small sample size.

Table 2. Univariate analysis

	Univariate OR (95% CI)
Age	1,003 (0,929-1,082)
Female gender	6,769 (1,605-28,542)*
Smoking	5,000 (1,363-18,348)*
Hypertension	3,222 (0,830-12,509)*
Diabetes	0,569 (0,134-2,409)
Hyperlipidemia	0,432 (0,115-1,622)

* $p < 0.1$ has been considered significant

DISCUSSION AND CONCLUSION

Subclavian artery stenosis can lead to serious morbidity, endangering the upper extremities, brain and the heart. Despite that, compared to other sites of atherosclerotic stenosis such as carotid or femoral arteries, the issue of SA seems somewhat neglected. The treatment for SA stenosis initially consisted of open surgery, developed in the 1950-s, carrying numerous complications with it. PTA followed in the 1970-s, but the issues of long term patency and restenosis remained a challenge. Since its introduction in the early 1990s endovascular procedure involving stenting proved to be an effective and popular treatment for SA stenosis, as well as for other sites. Its simplicity, effectiveness and shorter hospital stay coupled with fewer complications compared to open surgery make it appealing to physicians and patients alike ^{10, 13, 14, 15}.

Comparing this review with other similar studies ^{14, 15, 16}, most of the clinical and demographic indicators were inconspicuous. We observed a higher percentage of occlusions in our cohort (26%) compared to other studies (11% and 14%) ^{15, 16}. However, we detected a significant difference in the technical success rate. Technical success was achieved in 85% of the procedures in our center, whereas in other studies it was markedly higher, 93% in De Vries et al., 96% in Brountzos et al. and 98% in Patel et al. respectively. These differences may be due to the higher number of occlusions in our group of patients than in the compared studies.

Analysing comorbidities associated with the grade of stenosis only two well known risk factors were detected, hypertension and smoking ^{17, 18}. Female gender was identified as additional independent risk factor although the relevant literature indicates male gender as the risk factor ¹⁹. This may be due to the small sample size used for this analysis.

Although hyperlipidemia is a known risk factor for atherosclerotic stenosis, it did not reach statistical significance in univariate analysis. However, certain studies had so far observed protective effect of higher levels of high-density lipoprotein (HDL) against atherosclerotic stenosis ²⁰. It is important to note that the results of multivariate analysis are presented regardless of the small sample size.

To conclude, it appears that our patients correspond well with other patient populations considering risk factors, age at the time of procedure and comorbidities. However, this research provided a much needed insight into the effectiveness of interventions undertaken in our center. It is further important to assess the possible reasons for this discrepancy and the possibilities of improvement.

Finally, it is important to note that SSS is often overlooked and left undertreated, and yet the endovascular treatment is a simple and effective method, which when applied successfully can greatly improve the patient's quality of life.

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