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Munich, Germany

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Larissa - Ioannina, Greece

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[1]Department of Vascular Surgery, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece
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[1]Vascular Surgery Department, Attikon Teaching Hospital, National and Kapodistrian University of Athens, Athens, Greece
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[2]Guy's & St Thomas' NHS Foundation Trust, London SE1 7EH, UK - EU
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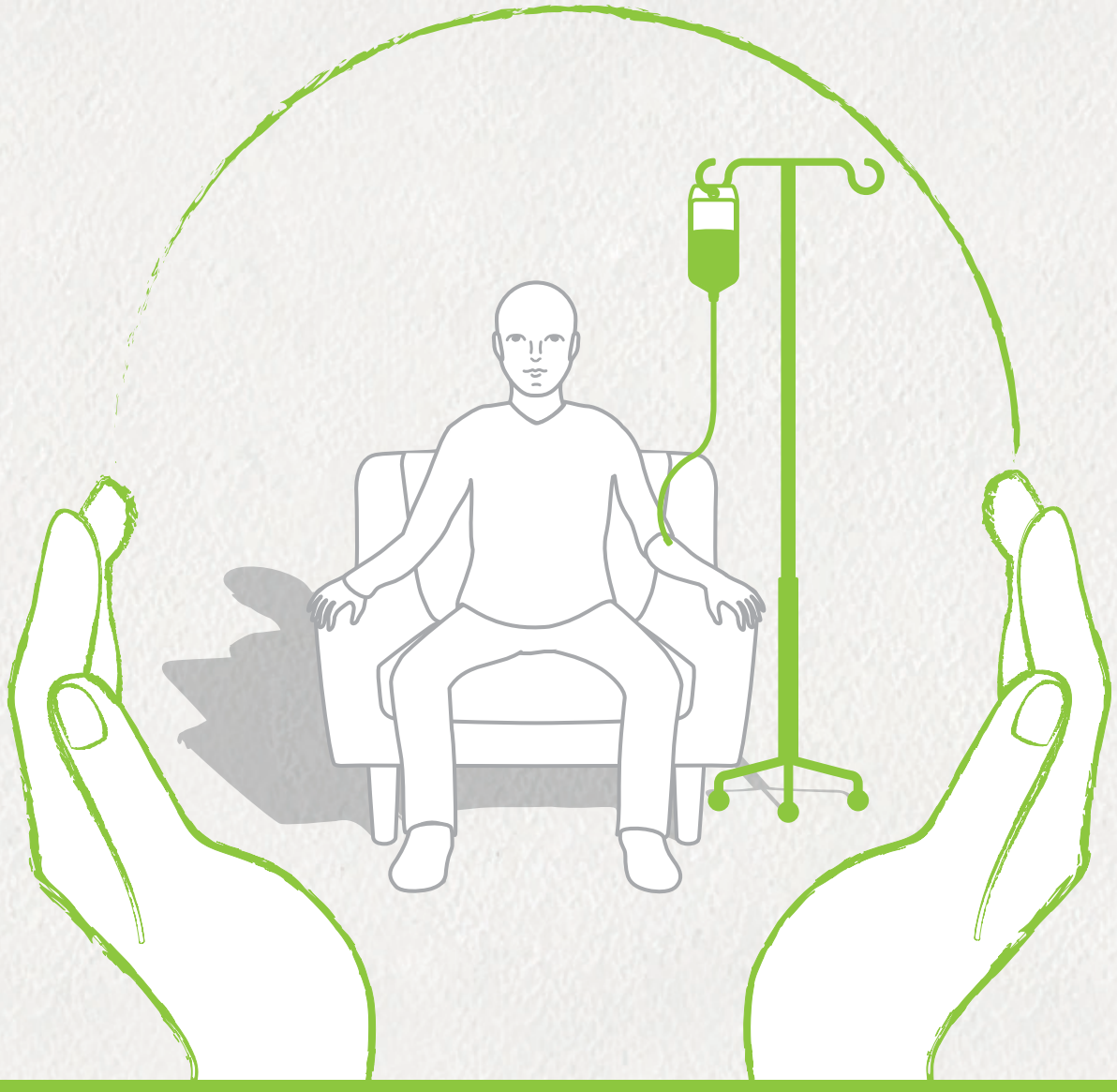

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EDITORIAL

Asymptomatic carotid artery stenosis

Hans-Henning Eckstein

Department for Vascular and Endovascular Surgery, Klinikum rechts der Isar, Technical University of Munich (TUM), Munich, Germany

About 15% of all ischemic strokes are caused by 50-99% stenosis or occlusion of the extracranial internal carotid artery. The overall prevalenve of a ≥50% carotid stenosis is about 4%. Smoking, increasing age, male gender, coronary heart disease (CHD) and peripheral arterial disease (PAD) are associated with an even higher prevalence of carotid stenosis[1]. Contemporary registries and randomized control trials (RCTs) indicate that the annual risk of a carotid-related stroke has decreased over time to 1-2% per year[2, 3]. Other reviews discriminated 50-70% from 70-99% stenoses and detected an annual stroke risk rate of 1.6% and 2.4% respectively[4].

According current guidelines a healthy diet, smoking cessation, and physical activity are recommended for all patients with asymptomatic carotid disease. Best medical treatment (BMT) consists of low-dose aspirin [75-325mg, or clopidogrel (75mg) if aspirin is not tolerated)], statins, antihypertensive treatment to maintain long-term blood pressure <140/90 mmHg and strict glycaemic control [5]. The European Society of Cardiology (ESC) specifies, that In patients with PAD (including carotid stenosis) the LDL-Cholesterol should be reduced to <1.8 mmol/L (70 mg/dL) or by >50% if baseline values are 1.8-3.5 mmol/L (70-135 mg/dL)[6]. A recent systematic review demonstrated a pretty high 2.9% cardiac-related annual mortality in patients with >50% asymptomatic carotid stenosis, confirming that these 'high-risk patients' should be treated agressively with statins[7].

A general duplex ultrasound (DUS) screening of the adult population is not recommended. However, clinical subgroups with an increased prevalence of carotid atherosclerosis (e.g. CHD, PAD) might benefit from DUS carotid screening. According to the current European Society for Vascular Surgery (ESVS) carotid guideline selective screening may thereby be considered in patients with multiple vascular risk factors to optimise risk factor control and medical therapy to reduce late cardiovascular morbidity and mortality[5]. Recent studies also indicate that the amount of 'carotid plaque burden' ('plaque area', or - even better - 'plaque volume') are associated with future cardiovascular risks[8, 9]. The BioImage study confirmed that a three-dimensional DUS assessment of carotid plaque volume is a valuable tool for cardiovascular risk prediction[10].

DUS is the main diagnostc tool for any extracranial carotid pathology, either for primary diagnosis or for follow-up examinations. In experienced hands the degree of stenosis, plaque extent and plaque composition can be assessed reliably. However, DUS is an observer-dependent imaging examination and internationally accepted standards for measurements (e.g. peak systolic velocity) are missing[11, 12]. Additional imaging measures [Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA)] are useful and sometimes necessary to confirm the degree of stenosis, to assess the degree of calcification [especially reasonable before carotid stenting (CAS)] and to detect lesions of the aortic arch or the proximal brain-supplying arteries. Furthermore, an incomplete circle of Willis could help to assess the collateral pathways in the presence of an ipsilateral high-grade carotid stenosis.

Due to the relatively low ipsilateral stroke risk rate in the natural course of carotid disease, carotid endarterecromy (CEA) or CAS should only be considered for subgroups of asymptomatic carotid patients with an increased late stroke risk. Based on a thorough analyis of the literature the recent ESVS and ESC guidelines evaluated the following clinical and imaging features that may be associated with an increased risk of late stroke in patients with asymptomatic 50-99% stenosis treated medically: history of contralateral transient ischemic attack (TIA) or stroke (Odds Ratio 3.0), ipsilateral silent infarction (OR 3.0), stenosis progression >20% (OR 1.92), spontaneous embolisation on transcranial doppler (TCD) (OR 7,5), impaired cerebral vascular reserve (OR 6,14), large volume plaques (>80 mm^2 as compard to <4mm^2, Hazard Ratio 5,16), predominantly echolucent plaques (OR 2,61), large juxta-luminal black area (>8 mm^2) and intraplaque hemorrhage detected by magnetic resonace imaging (MRI, OR 3,66)[5, 6].

In a meta-analysis of 2-3 years outcomes of the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial -1 (ACST-1), CEA + BMT had a significant stroke preventive effect in men (OR 0.49; 95% CI 0.36-0.66), but not in women (OR 0.96; 95% CI 0.63-1.45)[13]. Accordingly the 5-year results of ACST-1 demonstrated very clearly that CEA was associated with an absolute stroke risk reduction

Author for correspondence:

Hans-Henning Eckstein, MD, PhD, FEBVS

Department for Vascular and Endovascular Surgery, Klinikum rechts der Isar, Technical University of Munich (TUM), Munich, Germany

E-mail: HHEckstein@web.de

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of 6.5% within 5 years in men, as compared to women with a benefit of only 2.5% (statistically not significant). Only the 10-year data of ACST-1 demonstrated finally a significant stroke preventive effect of CEA also for women[14].

A recent systematic review analysed five randomized controlled trials [Veteran Affairs (VA)-Trial, Mayo-Study, ACAS, ACST-1, Aggressive Medical Treatment Evaluation for Asymptomatic Carotid disease (AMTEC)] comparing CEA plus BMT (2.633 patients) versus BMT alone (2.868 patients)[15]. The 30-day mortality and stroke rates after CEA + BMT versus BMT alone were 1.6% and 0.4% respectively. However, during follow-up CEA + BMT was associated with a significant lower risk of ipsilateral strokes (8.4% versus 13.4%, OR 0.59, 95% CI: 0.49-0.7). Only ACST-1 provided follow-up data >5 years and found a significance difference in favour of CEA (OR: 0.59, 95% CI 0.48-0.73). The mortality rate during follow up was 5.1% in the CEA group (2416 patients) and 6.6% in the BMT group (2418 patients) (OR 0.75, 95% CI: 0.59-0.96, P = 0.02), again in favour of CEA.

Several recent systematic reviews analyzed the 30-day and the long-term outcomes after CEA or CAS for asymptomatic carotid stenosis within RCTs. Whereas two SR[15, 16] did not detect any significant difference for 30-day stroke/mortality and the long-term stroke risks respectively, two other systematic reviews came to different conclusions. By excluding the SAPPHIRE trial (Stenting and Angioplasty with Protection in patients at high risk for endarterectomy)for methodological reasons Ciu et al[17] detected a significant lower periprocedural stroke risk (2.6% after CAS versus 1.26% after CEA, OR 0,53; 95% CI 0,29-0,96). The ipsilateral stroke risk was statistically not different (2.2% versus 1.2% respectively, OR 0,63; 95% CI 0,27-1,47).

A fourth systematic review[18] identified nine RCTs reporting on 3709 patients allocated to CEA. The stroke or death rate at 30 days was significantly higher after CAS (2.94%) compared with CEA (1.89%; OR 1.57; 95% CI, 1.01-2.44) The 30-day rates of myocardial infarction (MI) were statistically non-significant lower for CAS (0.66%) compared with CEA (1.50%). The incidence of cranial nerve injuries (CNI) at 30 days was significantly lower after CAS (0.11%) as compared to CEA (3.21%; OR 0.13; 95% CI, 0.07-0.26). The combined rates of stroke or death rate at 30 days plus ipsilateral strokes during follow-up were significantly higher after CAS (3.64%) than after CEA (2.45%, OR 1.51; 95% CI, 1.02-2.24). The authors concluded that there is moderate-quality evidence to suggest that CEA had significantly lower 30-day stroke and also stroke or death rates compared with CAS at the cost of higher CNI and non-significantly higher MI rates. The long-term efficacy of CEA in ipsilateral stroke prevention, was preserved during follow-up. However, more highquality research is needed to define the future role of CAS in the tretament of asymptomatic carotid stenosis.

Based on RCTs and SR the recently published ESVS and ESC guidelines gives almost similar recommendations to treat patients with an asymptomatic 60-99% carotid stenosis by CEA or CAS[5, 6]. Both societies agree, that the documented procedural risk of CEA and CAS in asymptomatic patients must be <3% and that the patient's life expectancy must exceed 5 years. ESVS and ESC agree also, that CEA or CAS shpuld only be considered if one or more imaging characteristics are present that may be associated with an increased risk of late ipsilateral stroke (see above). Unlike the ESVS the ESC adds that also *clinical characteristic* with an increased risk of late ipsilateral stroke should be considered, and that CAS should be (rather than may be) considered for patients deemed to be at high risk for CEA. The recommendations are the following:

- CEA should be considered for 'average surgical risk' patients (Class IIa, Level of evidence B).
- CAS may be an alternative to CEA for "average surgical risk" patients (Class IIb, LoE B).
- CAS may be (ESVS) / should be (ESC) considered in selected patients who have been deemed by the multidisciplinary team to be "high-risk for surgery" (ESVS: Class IIb, ESC: Class IIa, LoE B both)

Due to the relatively low risk of asymptomatic carotid stenosis treeated medically any revascularization has to be as safe as possible. Lokuge et al. analysed large observational studies. The authors demonstrated quite nicely that the procedural stroke/death rates of CEA for asymptomatic carotid stenosis decreased from 3.2% (studies before 2005) down to 1,5% (studies from 2005 onwards). In a meta-regression analysis, an 6.9% per annum reduction in CEA procedural stroke/death rates was detected. The procedural stroke/death rate of CAS (13 studies) however did not change significantly in asymptomatic patients between studies published before 2005 (2.9%) and from 2005 onwards (2.6%, p=0.628). The incidence of periprocedural MI did not change over time with rates of 1.1% and 0.6% after CEA and CAS repsectively[19].

In terms of future perspectives to further improve the management of asymptomatic carotid stenosis the following issues should be considered:

- An asymptomatic carotid stenosis is a marker disease for atherosclerosis. Therefore, all carotid patients need to be informed properly about the disease and non-medical measures. Furthermore, all carotid patients must be provided with BMT. Close follow-up examinations are mandatory.
- Current data indicate that CEA remains to be associated with slightly lower procedural stroke risks than CAS. MI and CNI occur more often after CEA.
- CEA and CAS should only be offered in centers, in which both modalities are availale. A neurological assessment before and after the procedure is recommended.
- CEA should only be performed by properly trained vascular surgeons, rather than by non-vascular surgeons[20-22]. CAS should only be perfomed by properly trained endovascular specialists[23]
- Volume outcome analyses indicate very clearly that CEA and CAS should only be performed in dedicated high-volume centers by high-volume vascular sur-

geons and endovascular specialists respectively[24, 25-28].

- A periprocedural stroke and death rate of 2% or lower (rather than 3%) seems to be achievable and should be adapated by future carotid guidelines.
- More and more CEAs are performed under loco-regional anesthesia (LA). In a recent analysis of the German Carotid Registry LA was associated with a relative risk reduction (RRR) of 15%. A brandnew analysis of the Carotid Stenosis Trialist Collaboration (CSTC) on >4.000 CEAs for symptomatic carotid stenosis demonstrates an even higher RRR of 30% (RR 0,70, 95% CI 0,5-0,99, Knappich et al., under revision). Is is thereby very likely that the awake patient constitutes a perfect intraoperative neurological monitoring[29].
- The value of intraoperative completion studies (DUS, angiography) is debated controversially. Data from the German Carotid Registry indicate that the use of DUS or angiography were associated with a statistically significant RRR of 26% and 20% respectively[29]. Since an "endproduct control" is an essential element of CAS, vascular surgeons should consider an intraoperative quality control as well!
- Due to guidewire manipulation, sheath passage, stent deployment and dilatation, almost all RCTs show, that transfemoral CAS under antegrade flow is associated with an increased risk of silent embolisation (up to 50% in diffusion weighted MR studies) and ipsilateral procedural strokes. Recent data indicate that transcarotid artery revasularization (T-CAR) with flow reversal could overcome some of these limitations and might achieve similar low complication rates as CEA in properly selected patients[30, 31]. This 'new kid of the block' might thereby be a real challenge for transfemoral CAS and possibly also a true alternative to CEA, however head-to-head data between T-CAR, transfemoral CAS and CEA are still missing. The same considerations apply for mesh-graft stents, again not enough data![32]

In conclusion, carotid disease diagnosed by DUS is a marker disease for the systemic disease 'atherosclerosis' Effective non-medical and medical treatment modalities are available. CEA (or CAS) should be considered for selected patients, in whom clinical or imaging variables indicate an increased future carotid-related stroke risk. More studies (e.g. plaque assessment, periprocedural measures, transcarotid stenting) are needed to continously improve the management of 50-99% asymptomatic carotid stenosis.

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Initial experience with the Nellix EndoVascular Aneurysm Sealing system for treating patients with abdominal aortic aneurysms: a case controlled comparative study

Konstantinos Mpatzalexis[1], George Kouvelos[1], Petroula Nana[1, 2], Konstantinos Spanos[1], Katerina Koutsothymiou[3], Eleni Arnaoutoglou[3], Athanasios Giannoukas[1], Miltiadis Matsagkas[1, 2]

[1]Department of Vascular Surgery, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece
[2]Department of Surgery-Vascular Surgery Unit, Medical School, University of Ioannina, Ioannina, Greece
[3]Department of Anesthesiology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

Abstract:

Background-Aim: The Nellix EndoVascular Aneurysm Sealing (EVAS) system is a novel approach to abdominal aortic aneurysm (AAA) endovascular repair whereby two PTFE stents deployed infrarenally, are used to exclude the aneurysm and biocompatible polymer is employed to fill and seal the AAA sac. The aim of this study was to assess the preliminary results of the Nellix stent-graft system and compare them with those obtained in patients treated with a well-established endograft of the same material and infrarenal fixation as the Excluder stent-graft.

Methods: A retrospective analysis of prospectively collected data from September 2014 to December 2018 identified 41 elective AAA patients treated with the Nellix endograft, in comparison to a matched group of 82 patients treated with the Excluder stent-graft. Endpoints included technical and clinical success, freedom from any secondary intervention, any type of endoleak and aneurysm related death.

Results: Primary technical success was achieved in all patients with null 30-day mortality. There was one limb thrombosis during the second postoperative day in the EVAS group. The Nellix group had lower levels of radiation burden, contrast media and duration of the procedure when compared to the Excluder group. During a median follow-up period of 23 months (range 1-53 months) there were no differences in clinical success, freedom from reintervention and aneurysm related death. One type Ib endoleak (2.4%) and three migrations (7.3%) were observed in the Nellix group requiring two reinterventions (4.9%). There were also six type II endoleaks, all in the Excluder group (7.4%), during the follow-up period (log rank=0.01). Five type II endoleaks resolved spontaneously, while in one patient the endoleak remained without any change in aneurysm sac diameter.

Conclusion: The initial experience with the Nellix stent graft system in the present cohort is quite promising, with successful aneurysm sealing and acceptable mid-term results, despite the current controversies. Further and larger studies are needed to fully evaluate the long-term results of this particular endograft.

INTRODUCTION

Endovascular aneurysm repair (EVAR) has gained wide acceptance as the primary treatment choice in patients with favorable anatomy.[1] Even though a marked benefit in perioperative mortality has been demonstrated in randomized controlled trials, such benefit decreases or even lost over time.[2] Aneurysm related adverse events such as endoleak and migration still occur consisting a challenge not only for the interventionists but also for the stent-grafts. Especially, type II endoleak (ETII) after EVAR seem a common finding and despite its usual benign course may sometimes lead to a worse outcome[3]. Endografts' manufacturers are constantly designing new devices to eliminate or even prevent complications related to EVAR.

In 2011, a novel concept of endovascular abdominal aortic aneurysm (AAA) treatment was introduced in clinical practice[4]. Endovascular Aneurysm Sealing (EVAS) technique, is characterized by obliteration of the aneurysmal sac by polymer-filled endobags, while maintaining the normal flow to lower extremities with two balloon expandable stent frames covered with expanded polytetrafluoroethylene. Its design aims mostly to reduce the rate of type II endoleaks, by using the filling of the aneurysm sac with the endobags to provide positional stability of the endograft and sealing of side branch flow. The single-piece conformation of the stents eliminates the threat of component separation and type III endoleaks.

Author for correspondence:

Miltiadis Matsagkas, MD, PhD, FEBVS

Professor of Vascular Surgery, Department of Vascular Surgery, Medical School, University of Thessaly, Mezourlo, Larissa, Greece
Tel: +30 6948585883
E-mail: milmats@gmail.com
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Other benefits of the system include reduced procedure times and radiation dose, respect to well established aortic stent grafts.[5-7] The early results of Nellix device where encouraging showing a high aneurysm exclusion rate and low frequency of endoleak and migration rates, even when used outside the original 2013 IFUs.[5-8]Despite this, in response to observations of device failure made in some early registries, the endograft's IFUs where progressively refined. In 2016, the new device's IFUs, narrowed considerably the range of morphological characteristics that render an aneurysm suitable for on-label EVAS.[9] Nevertheless, published data regarding safety and durability of the Nellix stent graft deployment in the long-term, still missing.

The aim of this study is to assess the early and mid term results of the Nellix stent graft system in terms of safety and durability and compare them with those of a well-established endograft as the Excluder (Gore & Associates, Flagstaff, AZ, USA).

MATERIALS AND METHODS

Study design

We conducted a case control study in order to evaluate the efficacy and safety of EVAS using the Endologix Nellix device. Between September 2014 and December 2018 472 patients with infrarenal AAA were operated. 41 (8.68%) of them were electively treated with EVAS using the Endologix Nellix device. The operations were conducted at the University General Hospital of Ioannina and the University General Hospital of Larissa. The patients' data were prospectively collected and inserted in a dedicated database including demographics, preoperative risk factors, operative time, contrast media use, patient outcomes, length of stay and complications.

All of the patients had AAAs with morphological characteristics suitable for endovascular repair. An informed consent was signed before the procedure.. Sizing and planning before the endovascular procedure were performed using a 3Mensio (Medical Imaging BV, Bilthoven, The Netherlands) dedicated reconstruction software.

The procedures were performed with bilateral femoral artery exposure under general anesthesia, or with ultrasound guided percutaneous catheterization. All interventions took place in an adequately equipped operating room using a BV Pulsera 12" mobile fluoroscopic C-arm unit (Philips Healthcare, Best, The Netherlands) and a radiographic carbon table equipped with side-table shielding (Varay Laborix, Bourges, France). The post-operative follow up protocol of the patients included physical examination and imaging control with a computed tomography angiography and/or a color duplex scanning at 1, 6, 12, and yearly after the procedure.

Technical aspects of the Nellix device

Nellix stent graft (Endologix, Irvine, Calif), is a sac-anchoring endoprosthesis which can be used to treat patients with adverse aortic neck and iliac anatomy as well as patients with standard neck and iliac anatomy. It consists of two balloon expandable stent frames covered with expanded polytetrafluoroethylene that maintain blood flow to lower extremities. The endoframes are surrounded by polymer-filled endobags which ensure the complete seal of the aneurysm, without the need of proximal and distal fixation of the endograft.[10,11] This way it anchors the endograft in the aneurysmal sac on one hand, while eliminates the space for endoleak on the other. In 2016 IFUs were refined to include a considerably limited range of anatomical eligible features for EVAS using the Nellix system. More specifically, the proximal maximum neck diameter reduced from 32 to 28mm while the distal maximum iliac diameter from 35 to 25mm. A new anatomical feature was introduced represented by the amount of thrombus in the aneurysmal sac. The thrombus ratio, resulting from the maximum aortic aneurysm diameter to the maximum aortic blood lumen diameter, according to the revised IFU, should be less or equal to 1.4. Such an indication wasn't taken in consideration at all at the original 2013 IFU.

Comparison group

The comparison group was selected from the sample of elective infrarenal EVARs using the Excluder stent graft during the same period. The Gore Excluder stent graft is a third-generation modern device featuring an original ePTFE design with a flexible catheter-mounted introduction and active infrarenal attachment with barbs. This endograft has the same fabric material as the Nellix endoframes while both have infrarenal fixation. In order to identify a control group with less selection bias, after the original cohort was formed, one of the investigators (G.K.), blinded to patient data apart from age, sex, and AAA diameter, matched the patients from the Nellix group 1:2 with individuals from the cohort treated with the Excluder endograft (112 patients, 23.7%). The two groups matched for age (<2 years), sex, and AAA diameter (<1 cm). The final population of this analysis included 123 patients, 41 patients in the Nellix and 82 patients in the Excluder group.

Outcome measurements

The definitions of the outcomes were established according to the reporting standards included in the guidelines of Society for Vascular Surgery/American Association for Vascular Surgery.[12] Technical success for both groups was defined as successful deployment of the endograft and completion of the procedure with no type I or III endoleaks and without the need for a secondary intervention within the first 24 hours. Clinical success was defined as freedom from aneurysm expansion >5 mm, type I or III endoleaks, aneurysm rupture, conversion to open surgery, graft infection, migration, or thrombosis, and aneurysm-related death during follow-up periods. PIS was defined as as the presence of fever (persisting body temperature >38_C lasting for >1 day during hospitalization) and leukocytosis (white blood cell [WBC] count >12,000/mL), with negative blood culture results.[13]

Statistical analysis

Data are expressed as mean ± standard deviation except for non-Gaussian parameters that are presented as median and

interquartile range. Categorical data are presented by absolute values and percentages (%). Statistical significance between the groups for continuous variables used the independent t-test for normally distributed data or the Mann-Whitney U-test for nonparametric data. The Pearson x^2 test or the Fisher exact test was used for categorical variables, as appropriate. Midterm follow-up data were analyzed by Kaplan-Meier life-table analysis, and results were compared by the log-rank test. Statistical analyses used IBM SPSS Statistics ver. 20.0 software (IBM Co., Armonk, NY, USA). A P-value of <0.05 was considered statistically significant.

RESULTS

Among 41 patients treated with EVAS, in 9 (21.9%) with suitable femoral artery anatomy, the endograft delivery occurred through percutaneous vascular access. Patient demographic data and preoperative risk factors are presented in Table 1. No significant differences in comorbidities were noted between the two groups.

The median aortic neck length was 26.5 mm in the Nellix group and 29.4 mm in the Excluder group (p=0.95). The median maximum diameter of the aneurysm in the respective groups was 56.8 mm vs. 57.6 mm (p=0.15). Angulations of the proximal neck were not significantly different between groups. Neck circumferential characteristics of >30% thrombus or >30% calcification were also statistically similar. There were 2 patients (5%) in the Nellix group with mild aneurysmal disease of the common iliac arteries (diameter <20mm) which were inside the original IFU. In the Nellix group, 40 patients were treated inside the Nellix IFU and only one outside. In the Excluder group all patients were treated inside the IFU of the specific endograft. In the Nellix group, 33 patients (80%) were treated according to the 2016 IFU and 7 patients (20%) according to the original IFU.

Perioperative data are summarized in Table 2. General anesthesia was used in all patients of both groups. The median operation time (p=0.04) as well as radiation burden (p=0.014) and contrast media used (p<0.001), were significantly lower in the Nellix compared to the Excluder group.

Technical success was achieved in all patients. No intraoperative conversion, migration, type I or III endoleak at the completion angiogram, or death were recorded at the end of the procedure. All renal arteries were patent at the completion angiography. No complications occurred in patients treated percutaneously. One patient with a significant common iliac artery tortuosity that has been underestimated suffered from limb thrombosis during the second postoperative day and was treated successfully with a fem-fem crossover bypass. Post implantation syndrome was encountered in 8.0% of the patients of the whole cohort with no differences between the groups (P=1). Median hospital stay was 3 days for both groups (P=0.49).

Baseline characteristics	Nellix group N=41	Excluder group N=82	p
Demographics			
Age (years), median (range)	72 (54-89)	73 (55-84)	0.8
Male gender (N,%)	40 (97)	80 (97)	1
Preoperative risk factors (N,%)			
Hypertension	25 (60)	58 (70)	0.69
Coronary artery disease	16 (40)	29 (35)	1
COPD	12 (30)	21 (25)	1
Hyperlipidemia	29 (70)	50 (60)	0.71
Diabetes	4 (10)	16 (20)	1
Cardiac failure	4 (10)	16 (20)	1
Smoking	12 (30)	25 (30)	0.69
AAA anatomy			
Neck length, mm	26.5 (16-60)	29.4 (15-60)	0.95
Suprarenal angle, degrees	7.5 (5-10)	9 (5-13)	0.28
Infrarenal angle, degrees	15 (10-40)	15 (5-40)	0.71
Maximum aneurysm diameter, mm	56.8 (51-96)	57.6 (50-93)	0.15
Thrombus >30%, N (%)	4 (10)	7 (8)	1
Calcification >30%, N (%)	8 (20)	13 (16)	1

Table 1. Baseline characteristics of the two groups

Perioperative characteristics	Nellix group N=41	Excluder group N=82	p
Procedure duration, min	80 (60-110)	98 (80-130)	0.04
Contrast media, ml	42 (30-80)	55.5 (30-110)	0.014
Radiation burden, mGy	80 (45-110)	102 (52.6-167)	<0.001
Post implantation syndrome, N (%)	3 (7)	7 (8.5)	1
Hospital length of stay, days	3 (3-6)	3 (3-5)	0.59

Table 2. Periprocedural data

During a median follow-up of 23 months (range, 1- 53 months), there were two reinterventions (4.9%) in two patients in the Nellix group and none in the Excluder group (log rank=0.09). None of the patients was lost to follow-up. One patient had bilateral large common iliac artery aneurysms, was treated outside the IFU with the Nellix device and showed a significant type Ib endoleak in both sides during the 6th month follow-up. He was successfully treated in two stages with two extensions to both external iliac arteries. No internal iliac artery embolization was performed, as there was a short distance between the external and internal iliac arteries' orifices and an adequate seal to both EIAs was accomplished.[14] He remains well at 2 year of follow-up with no symptoms of pelvic ischemia. One patient suffered a gradually significant (18mm) proximal graft migration without a type I endoleak at 24 months follow-up. Despite the absence of an endoleak we decided to treat the significant migration by endovascular means, extending the proximal sealing zone with an Altura (Lombard Medical, Oxfordshire,UK) stent graft. No graft-related deaths were recorded, while no conversion to open repair occurred. There were another two caudal migrations (7mm and 8mm) at 1 year and 2 years respectively without however a type I endoleak that remain under close surveillance. Six type II endoleaks (all in the Excluder group) were discovered during the follow-up period. Five endoleaks spontaneously resolved, while in only one patient the endoleak remained without any change in aneurysm sac diameter (log rank=0.01).

DISCUSSION

Type II endoleak (ETII) is a common finding up to 20% after EVAR and despite its usual benign course may sometimes lead to a worse outcome.[3, 15] There is a lack of level-1 evidence in this group of patients, and most studies are underpowered to fully understand the natural history of ETII due to the low event rate of complications and the inadequate long-term follow-up.[16] Even though an EII has a reasonable chance of thrombosing spontaneously, in some patients they might progress and result in sac enlargement and rupture.[3] To avoid such a worse outcome, these patients will need a reintervention. The Nellix concept aims to prevent type II endoleaks by completely excluding aortic collateral branches from the aneurysm sac. Sillingardi et al[17] presented a dual-center report of 64 patients treated with Nellix (2013-2014). During a median follow-up of 17 months, there was only 1 (1.6%) ETII noted. These results are in accordance with the findings of the present study showing a null type II endoleak incidence after EVAS.

In EVAR successful proximal infrarenal endograft fixation and sealing is critical to avoid both migration and endoleak complications. Several endografts have used different modalities to acquire AAA exclusion. The Nellix device fix the endograft in the aneurysmal sac on one hand, while eliminate the space for endoleak on the other. The Gore Excluder endograft, disposes an active proximal fixation mechanism. Adequate ovesizing and the presence of barbs incorporated on the proximal neck of the main body ensures the stent-graft's infrarenal fixation and prevents type Ia endoleak due to distal migration. Different clinical studies have documented the clinical outcomes and occurrence of type Ia endoleaks and/or migration after EVAS. In a multicenter retrospective cohort study conducted in Italy by Gossetti et al (IRENE study), at 1 year follow up period, the incidence of endoleaks reported, was 1.4% for type Ia, 0.7% for type Ib, and 1.1% for type II, with freedom from aneurysm-related reintervention rate at 94.7%18. Another multicenter retrospective observational study performed at six clinical centers in Europe and one in New Zealand, showed similarly, encouraging short term results. Böckler et al who carried out this study, involved 171 patients with AAA treated with EVAS. After a median follow up period of 5 months (range, 0-14 months), type Ia endoleak was observed in five patients (3%), type Ib endoleak in four patients (2%), and type II endoleak in four patients (2%) with aneurysm-related reintervention rate of 9% (15 patients).19 No aneurysm ruptures or open surgical conversions occurred. These studies suggest that endovascular aneurysm sealing with the Nellix device, appears feasible with high aneurysm exclusion rate and low overall complication and reintervention rates.

However, Harrison et al, in a retrospective review of 115 patients treated with Nellix endograft reported a 36.5% graft failure rate (caudal migration of the stents, separation of the endobags, and pressurisation of the sac). Only 19 patients treated in this cohort met the revised IFU for Nellix. Device failure was higher when used outside the original IFU (16.6 per 100-person years vs. 10.6 per 100-person years).[20] Additionally, in a Dutch retrospective study conducted by Zoethout et al involving 264 patients who underwent elective EVAS, 168 (63.3%) patients were treated within the IFU 2013 criteria; of these 48 (18.2%) were in compliance with the revised IFU 2016 version.[21] The rate of endoleaks within the IFU 2013 group was 5.4% (8 type Ia and 1 type Ib), whereas in the IFU 2016 subgroup was 2.1% (3 type Ia, p=0.583). In the present report we compared the behavior of the Nellix device with the behavior of an endograft with infrarenal fixation of the same material. During a median follow-up period of nearly 2 years, we found no significant differences in type I endoleak or migration occurrence between the two endografts. In the present study, patients were carefully selected according to the device IFU not having a complex unsuitable anatomy. This strategy may explain the acceptable short and mid-term results in comparison with the previously mentioned studies.[20, 21] For example, in the Harrisson et al study nearly one third of the patients were treated outside the IFUs, while a significant proportion of patients had complex anatomy for standard EVAR and had been turned down by other vascular centers.

The refined version of recommended IFU for the Nellix device was introduced in late 2016.[22] Zoethout et al by comparing 2-year clinical outcomes of patients treated within IFU 2013 and IFU 2016 found less complications, though not significant, in the IFU 2016 group when compared to the IFU 2013 group.[21] However, the applicability of Nellix has significantly reduced with the 2016 IFU, showing that this device seems not suitable for many AAA anatomies. In the present study 33 patients (80%) were treated according to the 2016 IFU; there were two reinterventions in one patient treated in-

side and one outside the 2016 IFU.

Radiation exposure during EVAR carries a potential risk toward patient safety.[23] In the present study EVAS showed a benefit by exposing patients to less radiation compared to EVAR. Ockert et al[24] and Antoniou et al[25] reported similar outcomes with reduced radiation exposure in EVAS compared to EVAR. This is useful to the patient as well as the operating team, in view of the cancer-causing risk associated to the radiation exposure.

The Nellix device is deployed through two 17 Fr (external diameter) tapered nose delivery catheters inserted via the femoral arteries. Hence, the delivery catheter diameter is adequate for percutaneous vascular access when femoral anatomy is suitable. In our study, 9 patients were treated with percutaneous EVAS while for postoperative artery sealing, a perclose vascular closure device was used (Perclose ProGlide, Abbott, Santa Clara, USA).

An important issue is represented by post implantation syndrome (PIS), the clinical and biochemical expression of an inflammatory response following EVAR. Both, the Nellix as well as the Excluder stent grafts are constructed of PTFE fabric supported by metal endoframes. Even if with lower rates than the polyester made stent grafts, it is possible for PTFE endografts to develop PIS.[26] Consistently to the literature, an overall rate of PIS was encountered in 8.0% of the patients, with no differences between the groups.

Computational fluid dynamics analysis aimed to study the flow conditions in the Nellix endograft, showed no significant alteration of the hemodynamic properties after the stent graft's implantation, resulting in optimal hemodynamic efficiency. [27]

In 2019 the CE mark for the Nellix device has been suspended following a voluntary recall and field safety notification issued by the company. This action reflects the 2019 ESVS guidelines recommending against the use of EVAS technique in clinical practice except when being used only within the framework of approved clinical studies.[1] The controversy found in the literature regarding the Nellix outcome in several studies maybe explained by the patient selection and doctor's experience. We may assume that due to the EVAS simpler applicability (lack of contralateral cannulation, less radiation and time), more doctors with less endovascular experience have used the platform with doubtful results. We believe that the proper selection according to specific anatomic criteria always within the IFUs is of paramount importance for achieving the best outcome when treating an AAA patient with EVAS.

The major limitations to the present study include its retrospective nature and the relatively small number of patients included in both groups. Despite this, all patients selected were treated consecutively with the Nellix stent graft system under stable conditions, and the case-controlled Excluder group was matched 2:1 to the Nellix group. In any case, these results must be interpreted with caution until validated by larger studies.

CONCLUSION

The initial experience with the Nellix stent graft system in the present cohort is quite promising, with successful aneurysm sealing and acceptable mid-term results despite the current controversies. Further and larger studies are needed to fully evaluate the long-term results of this particular endograft.

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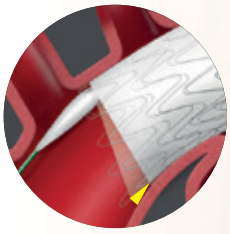

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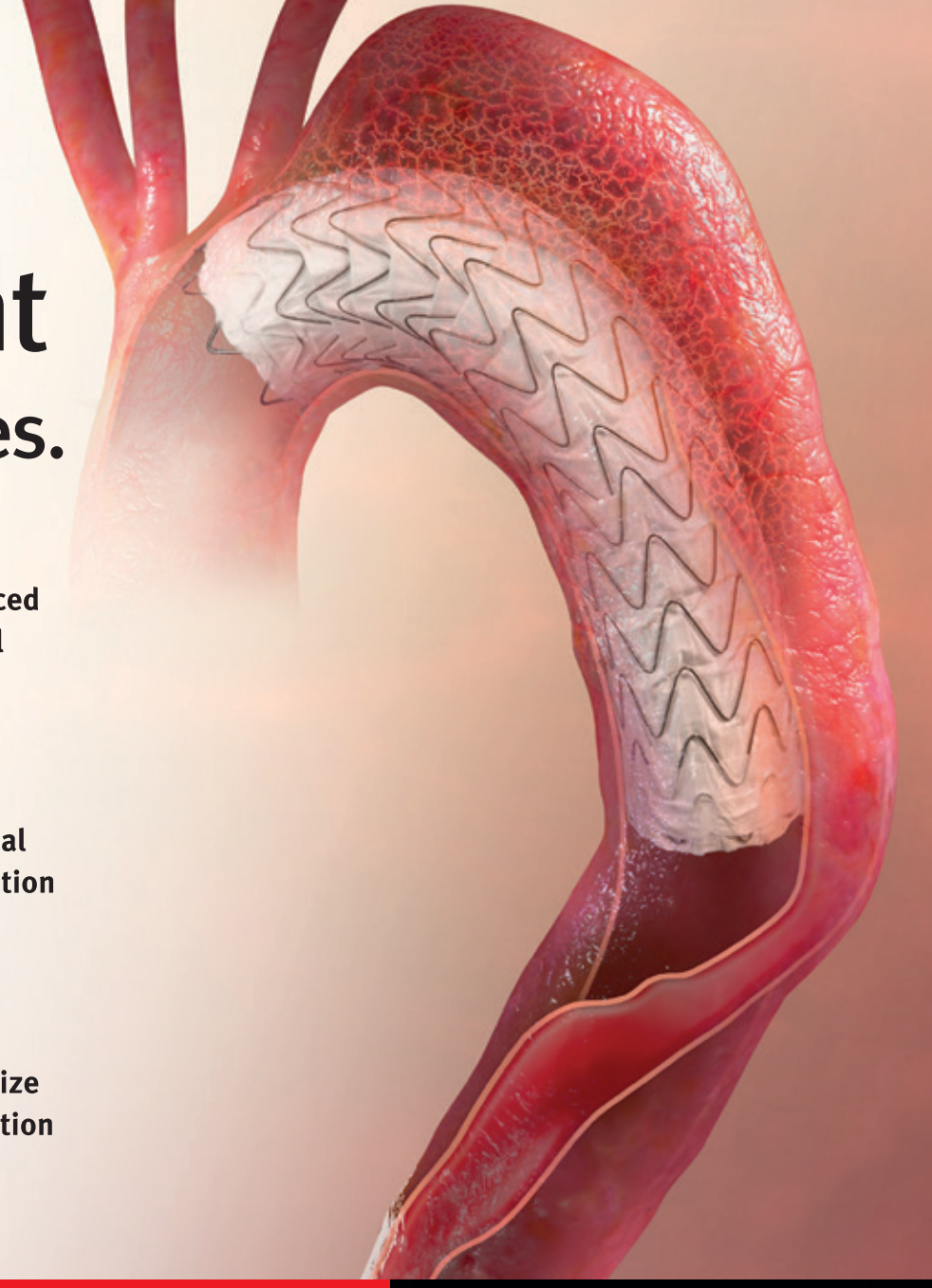

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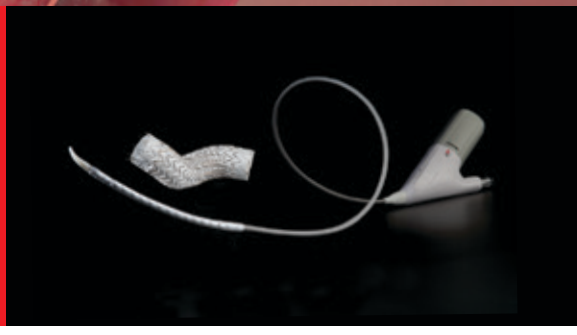

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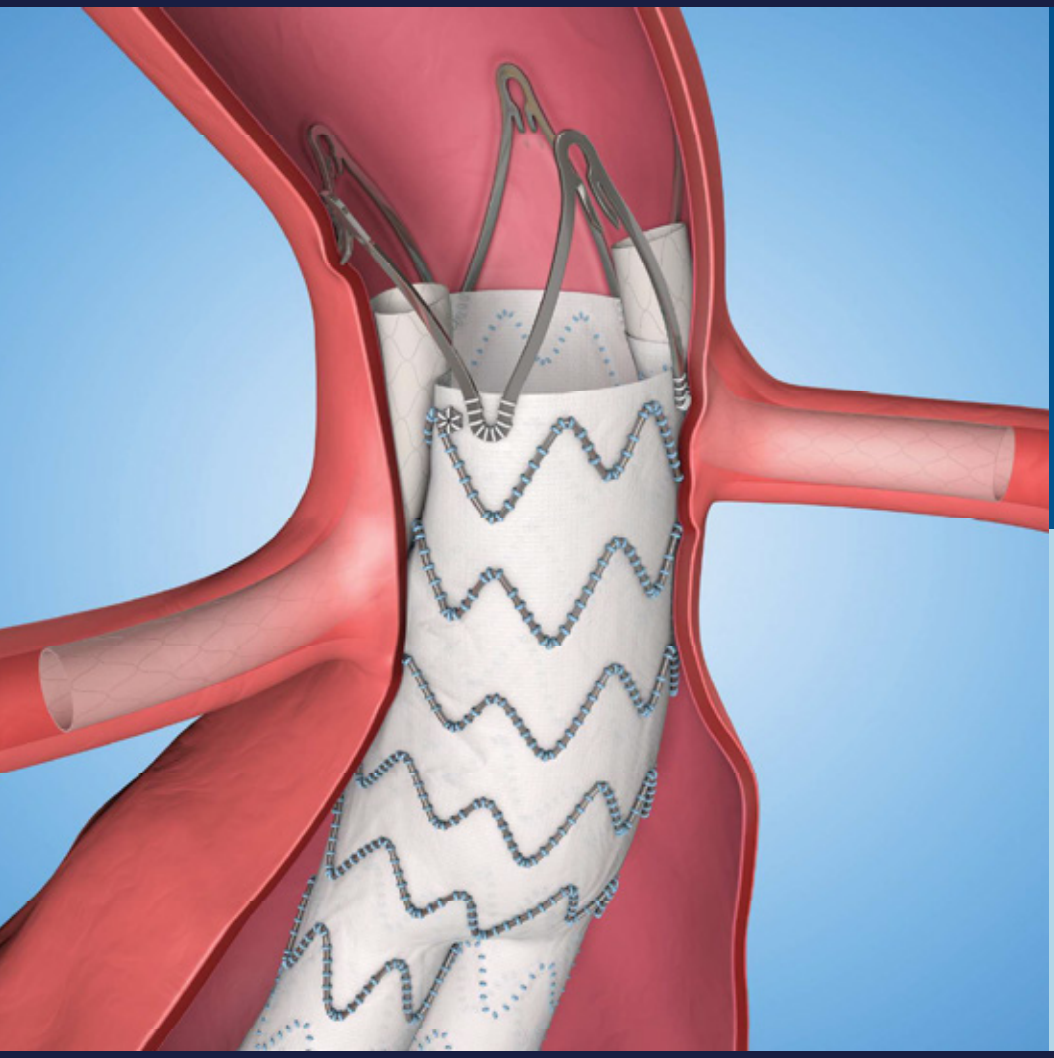

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Carotid Stenting Versus Endarterectomy for the treatment of carotid artery stenosis: Single center contemporary results

Petroula Nana[1, 2], George Kouvelos[1, 2], Eleni Arnaoutoglou[3, 4], Dimitris Xanthopoulos[1], Michalis Peroulis[1], Stavros Avgos[1], Stylianos Koutsias[1], George Papadopoulos[4], Miltiadis Matsagkas[1, 2]

[1]Department of Surgery-Vascular Surgery Unit, Medical School, University of Ioannina, Ioannina, Greece
[2]Department of Vascular Surgery, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece
[3]Department of Anesthesiology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece
[4]Department of Anesthesiology, Medical School, University of Ioannina, Ioannina, Greece

Abstract:

Background/aim: Although carotid endarterectomy (CEA) has long been considered the preferred intervention for carotid occlusive disease, carotid angioplasty and stenting (CAS) may serve as a minimally invasive alternative with equivalency in providing protection against ipsilateral stroke. The aim of the present study was tocompare the outcomesof both treatment modalities at a single center.

Methods: We retrospectively analyzed patients with carotid artery stenosis admitted to our hospital for carotid revascularization in a 14-year period. Eligibility criteria for revascularization were determined on the basis of symptomatic stenosis over 70% or asymptomatic stenosis over 80%. The primary outcome was a composite of periprocedural death, stroke, and myocardial infarction (MI).

Results: Of the 483 patients admitted for carotid revascularization 283 (58.6%) underwent CEA and 200 (41.4%) CAS. In total 301 CEAand 207 CAS procedures were performed. Symptomatic lesions were similar between the two groups, while no differences in baseline characteristics were found.In the CEA group, 30-day stroke rate was 0.9%. Major complications occurred in 3% of the procedures and cranial nerve injury in 4.3%. In the CAS group, technical success was 98.6%. Thirty-day neurological events included stroke in four patients (2%) and transient ischemic attack in two (1%). None of the patients in both groups died during the first 30 days. Both groups demonstrated similar rates of the composite outcome, MI, and death during the first 30 days after the procedure (p=0.34). During the follow-up period (mean 88±34 months in the CEA and 52±28 months in the CAS group) 15-year cumulative freedom from an ipsilateral stroke was 100% for both groups, while the 15-year cumulative freedom from any stroke was 88.4% for the CEA and 90% for the CAS group (p=0.643). 15-year cumulative freedom from restenosis was 98.3% for the CEA and 98% for the CAS group (p=0.353).

Conclusion: Short-term outcome, including stroke and myocardial infraction, was not differentbetween CEA and CAS in a single center providing both techniques. During follow-up, long-term protection against ipsilateral stroke did not also differ between the two methods.

INTRODUCTION

Atherosclerotic stenosis of the carotid artery is a major cause of ischemic stroke.[1] Carotid endarterectomy (CEA) has been used as tool for stroke prevention for many decades. The beneficial role of CEA in preventing strokes, mostly for symptomatic and to a lesser extent for asymptomatic patients, has been highlighted in all current guidelines.[2] In the era of less invasive procedures carotid artery stenting (CAS) has emerged as an evolving, less invasive, alternative technique that may even be used as first-line treatment in high-risk patients.[3] Randomized controlled trials comparing CEA and CAS have produced diverging results which may be at least partially explained by heterogeneity in patient's cohort, endpoint definition, operator experience and device immaturity.[3-6]

It has been shown that it is possible to achieve acceptable results with CAS at a single center, but not in a wider perspective.[7] Despite the quite inferior results of CAS in randomized, multicenter, prospective trials, the single center results support sufficiently both techniques, with similar event rates.[7,8,9,10] The strict criteria of patients' selection and the high-experience teams working in high-volume centers pro-

Author for correspondence:

Miltiadis Matsagkas, MD, PhD, FEBVS

Professor of Vascular Surgery, Department of Vascular Surgery, Medical School, University of Thessaly, Mezourlo, Larissa, Greece
Tel: +30 6948585883
E-mail: milmats@gmail.com
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viding both techniques may have probably affected the quality of those results.

The aim of the present study was to analyze all CEA and CAS procedures performed at our institution in a 14-year period with respect to efficacy, safety, and mid-term outcome.

METHODS

Study design

A retrospective study of all patients treated for carotid artery revascularization (CEA and CAS) from March 2001 to March 2015 at the University Hospital of Ioannina was conducted. CAS program was initiated on the January 2007. A dedicated database was established to prospectively collect patients' data, including demographics, preoperative risk factors, operative time, blood loss, contrast media use, patient outcomes, length of stay, and complications. Symptomatic patients included those with previous transient ischemic attacks (TIA) or strokes ipsilateral to the carotid lesion within the last six months. The degree of stenosis was evaluated by color duplex ultrasound imaging according to established NASCET criteria and confirmed by computed tomography angiography (CTA) of the aortic arch and intracranial and extracranial arteries.[11]

Eligibility criteria for carotid revascularization were determined based on symptomatic stenosis over 70% or asymptomatic stenosis over 80% and the presence of significant medical co-morbidities. CAS was contraindicated in case of total ICA occlusion, the presence of free-floating thrombus, severe chronic kidney disease (estimated glomerular filtration rate (e-GFR) < 30 ml/min) or contraindications against the use of dual antiplatelet therapy for at least four weeks.

The choice of revascularization method was at the discretion of the surgeon after a detailed preoperative evaluation. All patients signed an informed consent prior to the intervention and the study was approved by the institutional ethics committee.

CEA: CEA procedures were performed under general anesthesia, and a standard longitudinal incision with patch arteriotomy closure was undertaken in most cases (mostly bovine pericardium as patch material) (Figure 1). ICA stump pressure measurements in all patients and cerebral oximetry whenever available were used for intraprocedural assessment of cerebral collateral circulation to facilitate selective application of carotid shunting.[12] After returning to the ward and if there was no neurologic event as assessed by an independent neurologist or no other major complication, patients were usually discharged on the 2ndpostoperative day with aspirin 100 mg or clopidogrel 75 mg daily without imaging examination.

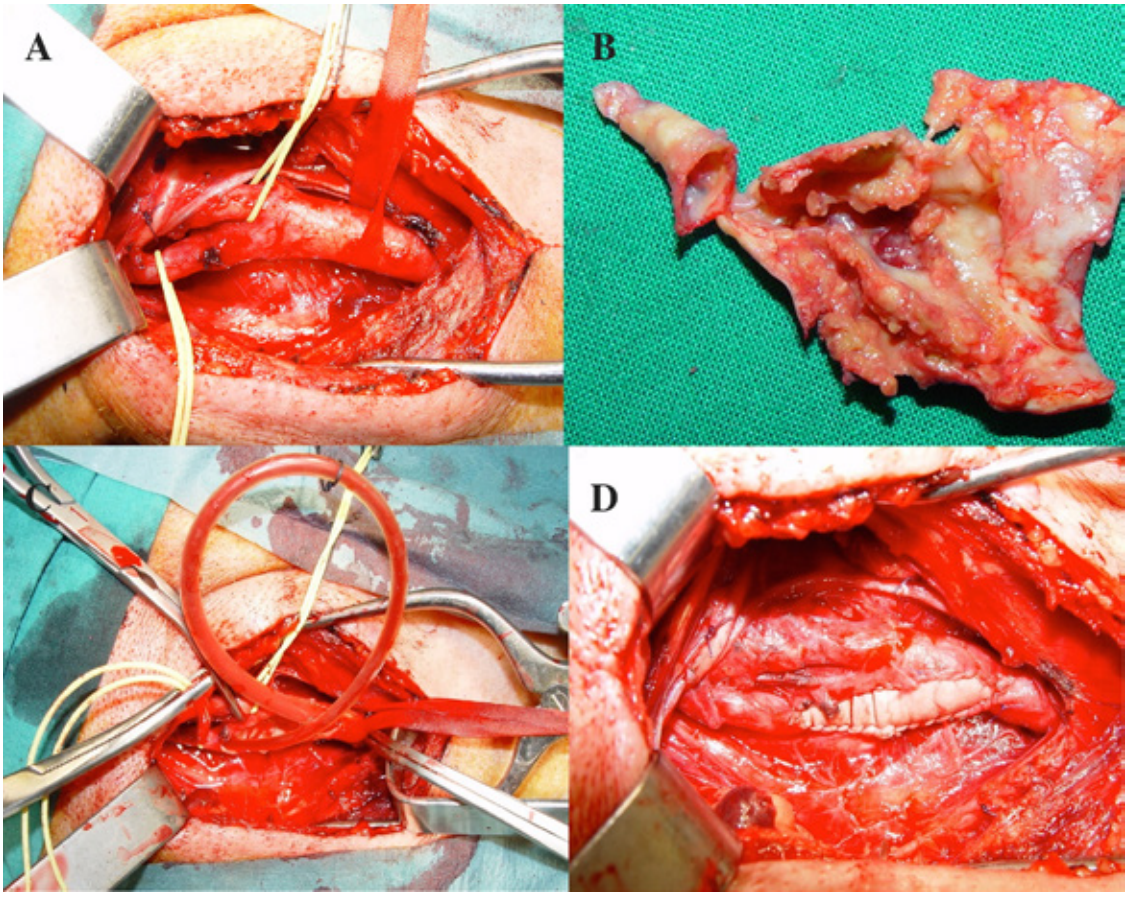

Figure 1. Carotid endarterectomy in a symptomatic patient (Panel A & B). A severe contralateral stenosis set the indication for shunt (Panel C). A bovine patch was used as a standard of care in most cases (Panel D).

CAS: CAS procedures were performed under local anesthesia in an operation theatre with the presence of an anesthesiologist. During the procedure unfractionated heparin was administered (50 IU to 100 IU per kg body weight). Access to the lesion was performed via the femoral artery using an 8F guiding catheter, finally positioned in the mid part of the common carotid artery. Most procedures were performed using distal ICA filters as cerebral protection devices. Following the placement of the protection device, the stent was deployed and post-dilatation performed with a balloon of 5 to 5.5 mm in diameter. In case pre-dilatation was needed, a 2.5-3.5 mm diameter balloon was used. (Figure 2) The choice of the stent was at the discretion of the surgeon (always tapered, open or closed cell design) and there was a preference of close-cell design for symptomatic lesions, according to the anatomy as well. Stenting was intended in every procedure and stent position typically extended from the common to the internal carotid, crossing the origin of the external carotid artery. Before retrieval of the protection device, final biplane angiogram of the stented lesion as well as intracranial views was obtained. Technical success was defined by the coverage of the carotid lesion with a stent in the presence of a residual stenosis < 30% and normal flow. During the CAS-procedure, all patients were monitored neurologically as well as for vital parameters under the care of the anesthesiologic team. After the procedure patients continued to receive dual anti-platelet therapy for at least one month and continued single antiplatelet agent thereafter.

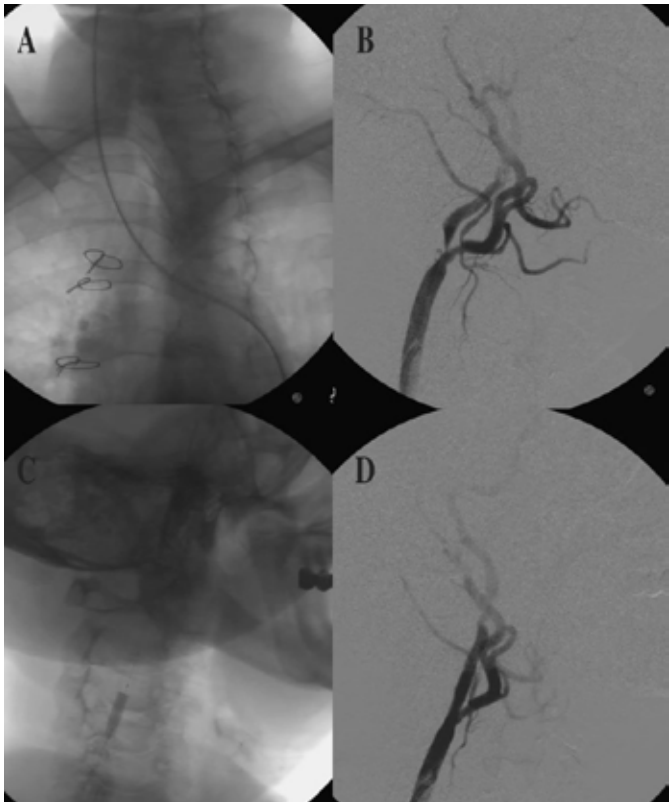

Figure 2. Carotid stenting in an asymptomatic patient with high grade stenosis (Panel A & B). Pre-dilatation was needed in this case (Panel C). Completion angiography confirmed a satisfying result (Panel D).

Outcomes

The primary outcome included 30-day major adverse events, including myocardial infarction (MI), stroke and death. Follow-up outcomes were stroke, myocardial infarction (MI), transient ischemic attack (TIA), death and rate of restenosis. TIA was defined as a new focal, retinal or hemispheric event that persisted for less than 24 h. Minor stroke was defined as focal neurological deficit lasting more than 24 h with Ranking score <2 and National Institutes of Health (NIH) Stroke Score <4, while major stroke was diagnosed in the presence of a Ranking score >3 or NIH score >15.[9] In-hospital surveillance was assessed by the treating therapist while in case of a new-onset adverse event, a consultation from a dedicated neurologist was demanded, According to neurologist evaluation, a CT or MRI (if available) was assessed to set the diagnosis. Clinical and duplex ultrasound follow-up visits to our outpatient clinic were routinely scheduled at 1, 6, and 12 months after the index procedure and yearly thereafter. Restenosis was diagnosed in the presence of a >50% ICA luminal narrowing as assessed by flow velocities using color duplex ultrasonography.[11]

Statistical analysis

Patients were analyzed according to the treatment they received. Data are expressed as mean ± standard deviation except for non-Gaussian parameters that are presented as median and interquartile range (IQR). Categorical data are presented by absolute values and percentages (%). Statistical significance between the groups for continuous variables used the independent t-test for normally distributed data or the Mann-Whitney U test for nonparametric data. The Pearson x^2 test or the Fisher exact test was used for categorical variables, as appropriate. Midterm follow-up data were analyzed by Kaplan-Meier life-table analysis, and results were compared by the log-rank test. Statistical analyses used SPSS 20.0 software (IBM Corp, Armonk, NY). A p value of <.05 was considered statistically significant.

RESULTS

Of the 483 patients admitted for carotid revascularization 283 (58.6%) underwent CEA and 200 (41.4%) CAS. In total 301 CEA and 207 CAS procedures were performed. 160 patients were treated with CEA between 2001 and 2006, and 123 between 2007 and 2015. The lower rate of CEAs after 2007 was due to parallel induction of CAS in our practice; from January 2007, we performed CAS liberally in much more patients, providing they had a suitable aortic arch, carotid lesion, and plaque anatomy, as well as all patients with an absolute contraindication for CEA (Figure 3). In a 9-year period, 207 CAS procedures were performed with an annual rate of more than 20 procedures per year.

	CEA group n=283	CAS group n=200	p
Patient characteristics			
Male gender	227 (81)	164 (81.2)	0.74
Age (years)	71.2±9.2	70.5±8.7	0.34
Risk factors			
Hypertension	170 (60)	130 (65)	0.30
Hyperlipidemia	164 (58)	137 (68.5)	0.09
Diabetes	43 (16)	42 (21)	0.10
CAD	85 (30)	75 (37.5)	0.18
COPD	86 (31)	59 (29.5)	0.32
Smoking	80 (28)	71 (35.5)	0.18
Lesion characteristics			
Side			
Left ICA	144 (48)	90 (44)	0.28
Right ICA	157 (52)	117 (56)	
Symptomatic lesions			
Stroke	60 (32.9)	35 (31)	
TIA	108 (59.3)	63 (55.7)	0.34
Amaurosisfungax	14 (7.8)	15 (13.3)	
Pathology			
Primary stenosis	301 (100)	207 (99)	0.78
Restenosis		2 (1)	

CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, ICA: internal carotid artery, TIA: transient ischemic attack

Table 1. Patient and lesion characteristics

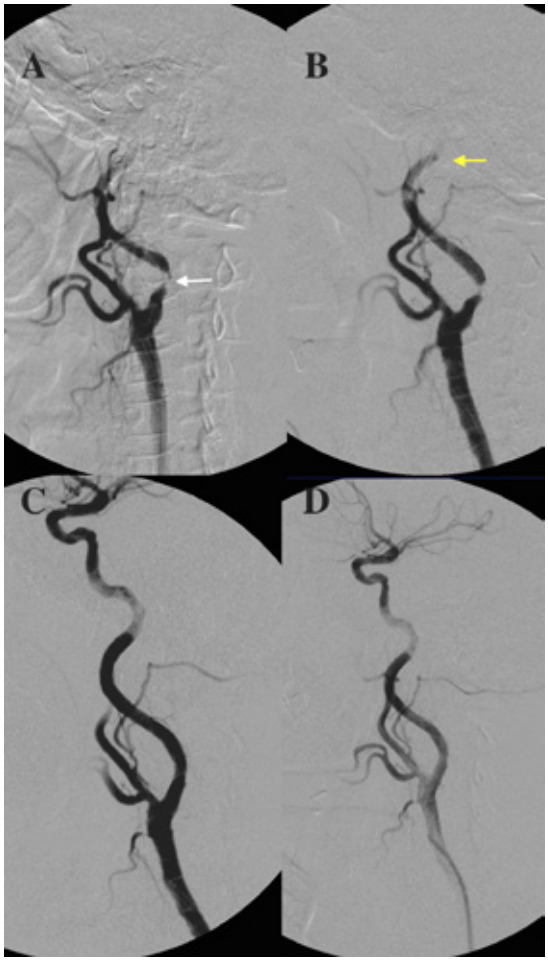

Figure 3. A symptomatic very high-risk patient treated with carotid stenting for a stenosis >90% (Panel A, white arrow). As embolic protection, a filter was used during the procedure (Panel B, yellow arrow). Completion angiography confirmed internal carotid artery patency (Panel C) and the restoration of the intra-cerebral circulation (Panel D).

CEA and CAS procedure data

CEA group: 182 carotid arteries (60.4%) were symptomatic and 119 (40.6%) were asymptomatic. 5 (2.7%) crescendo TIAs were included in the symptomatic group. Preoperative patients' characteristics are listed in Table I. All procedures were accomplished under general anesthesia, while the mean carotid clamp time was 33 ± 6.2 minutes (range 17-60 minutes).270 CEAs with patch closure (262 with bovine and 8 with polytetrafluoroethylene or Dacron patch) and 31 eversion CEAs were performed.

CAS group: Symptomatic stenoses were treated in 113 lesions (56.5%). All procedures were accomplished under local anesthesia, while in all patients' access was achieved through the femoral artery. Successful recanalization of treated vessel was obtained in 204 cases (98.6%). There were three technical failures. In one patient we were unable to deploy the embolic protection device distally to the lesion due to severe ICA kinking, while in another patient common carotid artery catheterization was failed due to the presence of hostile aortic arch. The third patient had a nearly occluded ICA characterized by a calcified irregular plaque and we were not able to cross the lesion. All three patients were converted on site to CEA under general anesthesia with a good clinical result.

	Symptomatic	Asymptomatic	p
CEA group			
Stroke	3 (1.6)	0	<0.001
TIA	0	0	NA
CAS group			
Stroke	4 (3.5)	0	<0.001
TIA	1 (0.8)	1 (1)	0.34

TIA: transient ischemic attack

Table 2. Patients' 30-day outcome according to the presence of symptoms

Embolic protection devices (EPD) were applied in all technically successful procedures (Table 3) CAS. The vast majority (98.5%) included filter devices, while balloon occlusion devices were used in only 3 patients. The lesions were pre-dilated in 37 cases (18.1%) and post-dilated with a balloon in all procedures. Stents were applied in all lesions. One stent per procedure was used in 197 lesions (96.6%), while in 7 lesions the use of two stents was necessary, due to long carotid lesions (4 cases), or extensive jumping of the first stent (3 cases). Stents with an open cell design were deployed in 118 patients, while closed cell stents in 86 patients. Symptomatic patients were more likely to receive a stent of closed cell design (p<0.001).

	n (%)
Type of stent	
Acculink (Abbott)	96 (44.1)
X-act (Abbott)	41 (19.2)
Exponent (Medtronic)	22 (10.3)
Adapt (Boston)	33 (15.5)
Protégé (Covidien)	12 (5.7)
Wallstent (Boston)	7 (3.3)
Crystalloo Id (Invatec, Medtronic)	4 (1.9)
Type of EPD	
Accunet (Abbott)	81 (39.8)
Emboshield (Abbott)	54 (26.7)
Interceptor+ (Medtronic)	29 (14)
Filterwire (Boston)	37 (18)
Moma (Invatec, Medtronic)	3 (1.5)

EPD: embolic protection device

Table 3. Procedural characteristics

Outcome: 30-day stroke rate was 0.9% in the CEA and 2% in the CAS group (p=0.112). Symptomatic patients were more likely to suffer from stroke during the peri-procedural period than asymptomatic patients in both groups (p<0.001). Mortality was null in both groups. ***In the CEA group*** there were 3 strokes. One symptomatic male patient had an acute ICA thrombosis during an episode of paroxysmal atrial fibrillation with hemodynamic instability. Re-exploration was not attempted because of the patient's severe condition and multiple intracranial carotid lesions. The patient recovered from kinetic problems but not from aphasia and died after 28 months due to a cardiac event. The second stroke concerned a symptomatic male patient with contralateral ICA occlusion. The operated ICA remained patent and the CT scan negative, so it was considered a lacunar stroke. The patient recovered completely and remains alive with patent ICA almost 13 years after the procedure. The third stroke occurred in an asymptomatic female patient who suffered an acute ICA thrombosis. Re-exploration revealed an intimal flap at the proximal site of the CEA. The defect was repaired and the ICA successfully recanalized. The patient recovered completely from the stroke and is alive with patent ICA 7 years after the procedure. ***In the CAS group***, four patients, all symptomatic, suffered an ipsilateral stroke. All these strokes were minor and none of them became disabling through the hospitalization period. Two (1%) patients, one symptomatic and one asymptomatic, suffered a TIA, while in two other patients, cognitive dysfunction observed after the operation that completely resolved after 1-3 days. No significant relation was shown between the cerebrovascular event occurrence and the type of stent (stroke, p=0.405; TIA, p=0.624). No access-site pseudoaneurysm was diagnosed in any patient, expect of 5 cases of post-operative mild hematoma with no clinical significance which were treated conservatively.

In the CEA group, rate of complications was 3.6% including 7 cardiac (5 acute coronary syndromes and 2 paroxysmal atrial fibrillation), 1 pulmonary (acute respiratory insufficiency), and 1 renal (acute renal failure); 2 patients experienced neck hematoma, requiring drainage under local anesthesia due to airway compression. Median hospital in-stay was 2 days.12 (4%) postoperative events of cranial nerve injury were observed; 6 were related to the hypoglossal and 6 to the inferior laryngeal nerve. In 11 patients, symptoms were revealed during the first 6 months' follow-up, while in only 1 remained as vocal cord paresis without significant clinical consequences. ***In the CAS group,*** there were no cardiovascular events or major complications within 30 days. Median hospital in-stay was 2 days.

FOLLOW-UP

The mean follow-up time was 88 ± 34 months (range12-168 months) for the CEA and 52±28 months (range 18-98 months) for the CAS group. 52 patients (10.6%) in the CEA and 24 patients (12%) in the CAS group were lost to follow-up. The latest recorded data for all patients were used for the analysis.

Cerebrovascular events: Twenty patients, 12 in the CEA and 8 in the CAS group, experienced a late stroke. All late strokes were contralateral to the operated carotid, and 6 were fatal. The15-year cumulative freedom froman ipsilateral stroke was 100% for both groups, while the 15-year cumulative freedom from any stroke was88.4% for the CEA and 90% for the CAS group (log rank test=0.215, p=0.643, (Figure 4A).

Restenosis: Five carotid arteries, 4 (1.3%) in the CEA and 1 (0.5%) in the CAS group, developed restenosis at 3, 12, 18, 36 and 24 months, respectively. All patients with restenosis remained asymptomatic. In the CEA group, one restenosis progressed to total occlusion and 3 in significant lumen stenosis (> 50%), but only 1 case required an endovascular intervention due to severe (> 90%) narrowing. The other 2 patients remained under surveillance. In the CAS group, there was an in-stent restenosis in the mid portion of the stent that was progressed in >90% after 2 more years. This patient was successfully treated by CAS again, using a balloon expandable short stent this time. 15-year cumulative freedom from restenosis was 98.3% for the CEA and 98% for the CAS group (log rank test=0.862, p=0.353, Fig. 4B).

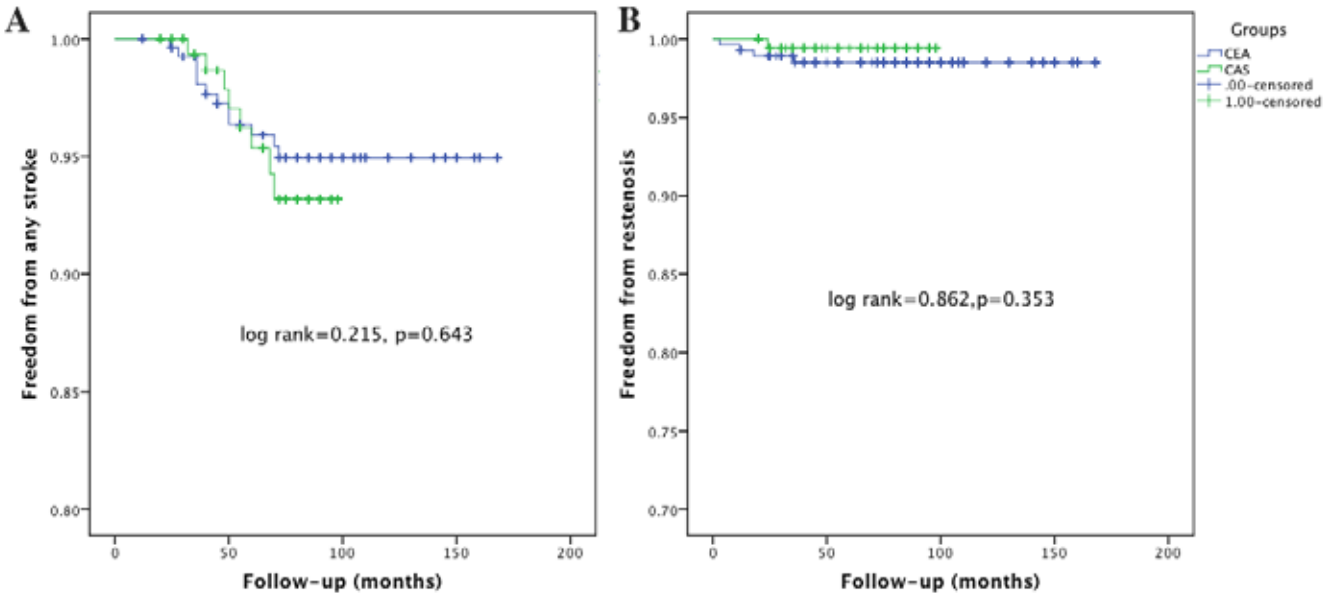

Figure 4. Kaplan-Meier cumulative proportions of freedom from any stroke (A) and for restenosis (B) for both groups of patients.

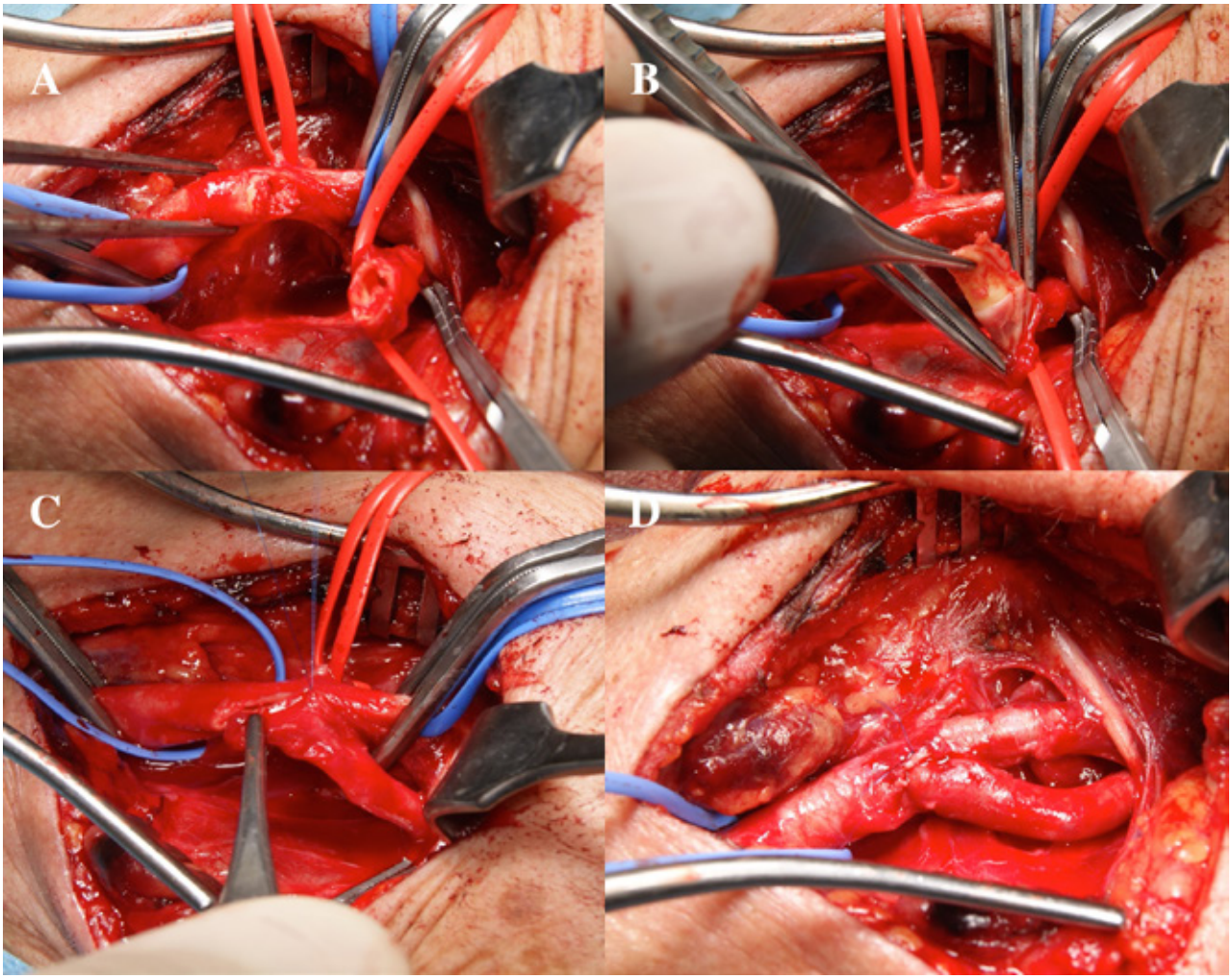

Figure 5. Carotid endarterectomy with the eversion technique (Panel A & B). Eversion technique has analogous results concerning restenosis as patch closure (Panel C & D).

DISCUSSION

In the largest and most reliable randomized trial of CEA vs CAS, CEA conserved its superiority in the prevention of stroke, particularly in symptomatic patients (Figure 5).[6] This study showed a higher rate of stroke in patients treated by CAS during the 30 days after the procedure. Respectively, a higher rate of cardiac events was recorded for patients treated by endarterectomy. Similar to CREST, in our study, there were no significant differences in the occurrence of the composite endpoint, consisting of major stroke, MI, and death but patients undergoing CAS did demonstrate a higher rate of periprocedural stroke, although non statistically significant.[13] This was likely related to the fact that patients undergoing CAS tended to have more baseline medical comorbidities.

In a meta-analysis of 21 published registries and nearly 1.500.000 patients, the stroke and death rate following CAS remained significantly higher than after CEA and remarkably exceeded the threshold referred in current guidelines.[13,14] In 43% of the analyzed registries for asymptomatic and in 72% registries for symptomatic patients, the stroke/death rate was over the 3% and6% AHA/ASA guideline threshold respectively.[14] However, these data included patients even from the first CAS years when EPD were not routinely used while some of them suffered from reporting and selection biases.[14]

On the other hand, data from single center studies offering both CEA and CAS seem promising. In a recent single center report of nearly 500 patients, the incidence of in-hospital stroke and death was below 1%, while in another single vascular surgeon report offering both modalities no differences were noted with low rates of periprocedural stroke (2% CEA vs 1.2% CAS).[8,15] The results of the present study show that in selected patients and in single centers with a high operational experience, there is no significant difference between the two methods. In symptomatic group, we confirmed a higher post-operative stroke rate than asymptomatic patients, with an occurrence rate much less than the 6% guideline benchmark. Equally, in asymptomatic patients the stroke rate was much less than the 3% benchmark, even in patients treated with the CAS technique. These single center results of carotid artery disease treatment could be explained by the factor of operator's competency. In experienced high-volume centers the results seem to be different and much better than those mentioned in multicenter trials. The strict criteria in patients' selection and the high experience of operating teams on both techniques could offer a patient tailored approach that may lead to a better outcome.

Long-term prevention from neurologic events constitutes the hallmark of effective carotid revascularization. During the follow-up period none of our patients sustained any ipsilateral cerebrovascular event. These results are in coherence with those reported in randomized studies that have demonstrated the same low mid-term stroke rate with no significant differences between CAS and CEA.[16,17]

There were several limitations to this study. This study reports data from a single center, is hypothesis generating and due to its retrospective nature lacks power to draw widely applicable conclusions. In addition, the study lacked randomization and cannot account for selection bias. All procedures were performed by the same surgical and anesthesiology team. The results of this study only apply to the population of patients with carotid artery stenosis admitted to our hospital and cannot be generalized across institutions with varied procedural experience. Furthermore, the relatively limited number of patients does not allow a reliable subgroup analysis for detection of patient or lesion's characteristics that may account for a different risk for cerebrovascular events and certainly the possibility for a type II statistical error cannot be excluded.

CONCLUSION

Short-term outcome, including stroke and myocardial infraction, was not different between CEA and CAS in a single center providing both techniques. During follow-up, long-term protection against ipsilateral stroke did not also differ between the two methods. More real-world comparative data outside RCTs and registries are needed to define the role of each technique in treating patients with significant carotid artery stenosis.

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INVITED COMMENTARY

In the era of large randomized control trials for carotid artery disease, do real-world data offer additional information?

Andreas M. Lazaris[1], Konstantinos Moulakakis[1], George Sfyroeras[1], Vangelis Alexiou[1], George Tsivgoulis[2], George Geroulakos[1]

[1]Vascular Surgery Department, Attikon Teaching Hospital, National and Kapodistrian University of Athens, Athens, Greece
[2]2nd Neurology Department, Attikon Teaching Hospital, National and Kapodistrian University of Athens, Athens, Greece

The study of Nana et al.[1] presents real-world data regarding carotid endarterectomy (CEA) and carotid artery stenting (CAS) of a single center experience. According to the authors, CEA and CAS can have excellent short, medium and long-term results when performed in properly selected patients by an experienced surgical and anesthesiological team that follow a well-established standardized practice protocol. No significant difference exists between CEA and CAS as it concerns the 30-day stroke/death rate, either in the total cohort of patients (0.9% for CEA vs. 2% for CAS), or separately in symptomatic (1.6% for CEA vs. 4.4% for CAS) and asymptomatic patients (0% for CEA vs. 1.1% for CAS). Similarly, no differences are noticed in the long-term (15-year) follow-up, both in freedom from an ipsilateral stroke (100% in each group), or from any stroke (88.4 for CEA vs. 90% for CAS).

Following the 2011 American Heart Association / American Stroke Association (AHA/ASA) Guidelines, CAS was considered an alternative to CEA.[2] This was based mainly on the results of CREST trial,[3] and suggested that CEA or CAS can be performed in symptomatic and asymptomatic patients as long as the accepted rates of perioperative death/stroke are met (6% in symptomatic and 3% in asymptomatic ones). This was replicated in the 2017 ESVS guidelines.[4] However, registries and audits from various vascular societies throughout the world representing real-world data, report worse death and stroke rates than in the randomized controlled trials (RCTs). In a systematic review of large administrative dataset registries of patients who had CEA or CAS, almost three quarters of registries reported procedural risks after CAS well in excess of the 6% recommended risk threshold in symptomatic patients.[5]

Nevertheless, single centers with high-level of expertise of both surgical and anesthesiological teams seem to offer exceptional results in properly selected patients. It is known that increased experience improves results after CAS.[6] On the contrary, poor exposure is related to inferior results for both CEA and CAS. Definitely, a high-selection in favor of low-risk patients which may be the practice of a specific surgical team or a medical center can offer better results with a reduced stroke rate, despite the fact that this may not be translated in saving more patients from a recurrent stroke. Time to intervene after a TIA or minor stroke is a factor that can contribute to this paradigm. In a meta-analysis of population-based studies, Giles et al observed that the risk of stroke at 2 days after a TIA was 6.7% and at seven days 10.4%.[7] On top of that, Rothwell et al,[8] based on their predicting scoring system, supported that in case of elderly (more than 60 years of age), hypertensive population, a TIA or minor stroke presenting with unilateral weakness of more than 60 minutes duration incurs a risk of recurrent stroke at seven days of 31.4%. Interestingly, the model was replicated by Tsivgoulis et al.[9] who noticed that the risk of stroke in this group of patients may be up to 31.3% at 30 days after a TIA. These observations indicate that the first few days (less than 14) after the index event are those that are the most crucial for a recurrent episode. Unfortunately, these are the days that is most possible to have an undesired cerebrovascular event, after a revascularization attempt, either open or endovascular. Nevertheless, it seems that performing CEA or CAS within the first 14 days after the stroke event with a 10% procedural risk will actually prevent more strokes at 5 years than waiting 4 weeks and then intervening with a 0% procedure risk.[10] Thus, time of intervention after the ischemic event is crucial in symptomatic carotid artery disease management, and it should be documented. In the current study by Nana et al, although a large percentage of patients were symptomatic, larger than what is described in most of RCTs comparing CEA with CAS, no specific data regarding the time-interval from the event to intervention are presented.

Definitely, results from population-based studies add to the current knowledge of carotid artery disease management as long as data recording follows certain rules. This can become a reality when adapting specifically designed audits and registries in the current medical practice. Uniform registries that report the catholic practice with a unique way of documentation will provide us with all the necessary information to assess the medical practice compliance to the guidelines, this leading to reducing mistakes and improving outcomes. Based

Author for correspondence:

Andreas Lazaris, MD, FEBVS, FACS

Associate Professor of Vascular Surgery, Department of Vascular Surgery, Attikon Hospital, Athens, Greece
Tel: +30 6977436576
E-mail: andreaslazaris@hotmail.com
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on the current practice in most of the modern health systems, the Hellenic Society of Vascular and Endovascular Surgery has endorsed the creation of HEVAR(Hellenic Vascular Registry).[11] HEVAR will hopefully become the mean of data collection of, among others, CEA and CAS. When results of large number of patients treated with either CAS or CEA from Greek hospitals are obtained, then an established overall conclusion regarding the current vascular practice on carotids could be made. Hopefully, this may the beginning of a new era, with a plethora of data regarding among all and the carotid artery disease.

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Stenting for restenosis after prior carotid endarterectomy may be safely performed: a retrospective cohort study

Christiana Anastasiadou[1], Demetrios Tzortzis[2], Anastasios Papapetrou[1], Nikolaos Zannes[2], George Kastrisios[1], Sotirios Giannakis[1], Chrisostomos Maltezos[1]

[1]Vascular Surgery Department - "KAT" General Hospital of Attica, Greece
[2]Interventional Radiology Department - "KAT" General Hospital of Attica, Greece

Abstract:

Carotid endarterectomy (CEA) is the treatment of choice for carotid artery stenosis, especially for young patients with low or average surgical risk. However, for patients who present with restenosis the therapy of choice remains debatable. We present our experience treating restenosis after CEA with carotid artery stenting (CAS), suggesting that stenting may be safer for the patient. Moreover, we identified some characteristics present among patients with restenosis, such as female gender, low HDL levels, increased fibrinogen and increased BMI.

INTRODUCTION

Carotid endarterectomy is the therapy of choice for significant carotid stenoses, especially in young patients with low or average surgical risk. Generally, restenosis is considered a benign condition when compared to primary atherosclerosis of carotid artery and therefore, it remains controversial if an asymptomatic restenosis should be treated medically or by CEA/CAS. Nevertheless, patients with post CEA restenosis could be considered for treatment too, as they acquire higher risk of late ipsilateral stroke compared with patients with no restenosis and with patients with restenosis following CAS.[2,3] Treating strategy includes CEA or CAS, as both demonstrate similar periprocedural stroke/death rates. However, re-do CEA is technically demanding and implements an increased risk for cranial nerve injury (CNI).

We present the experience in a Greek tertiary hospital, treating post-CEA restenosis solely with stenting, and we propose the reasons we consider CAS is superior in restenotic carotid arteries.

Author for correspondence:

Christiana Anastasiadou

Nikis 2, Kifisia, P.O 14561, Greece
Tel: +30 6949722390, +30 2132086069
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METHOD

We performed a retrospective analysis of data collected from patients treated for carotid artery disease between January 2017 and December 2018. Baseline characteristics, demographics and risk factors are presented in Table 1 whereas periprocedural data are presented in Table 2. The diagnosis of restenosis was defined in all patients using duplex scan ultrasonography.

Procedure: We performed computed tomography angiography to assess the atherosclerosis of the aortic arch and the carotid arteries. Informed consent was obtained, orally administrated clopidogrel and aspirin was given before treatment. Under local anesthesia and through a transfemoral approach, an angiogram of arch was obtained, and a selective common carotid artery angiogram was performed confirming the diagnosis (Fig. 1). The patient received 5000 units of heparin as a bolus intravenous dose. CAS was performed without utilizing embolic cerebral protection device in most of the cases. A self-expandable stent across the stenosis was used in all cases. Post-dilation with a 5-mm balloon was performed and final angiogram confirmed the satisfactory result (Fig. 2). Atropin and mannitol were not given on a routine fashion

GENDER	AGE	SURGERY	TIME TO REINTERVENTION	SMOKING	DM	CAD	FIBRINOGEN	BMI	ANTIPLATELET	HDL	SYMPTOMS	STATIN	HYPERTENSION
F	65	CEA SYNTEHTIC PATCH & SHUNT	1 YEAR	NO	YES	YES	HIGH	31	DUAL	LOW	NO	YES	YES
F	52	CEA SYNTEHTIC PATCH	8 MONTHS	NO	NO	NO	HIGH	23	A	LOW	NO	YES	YES
M	58	CEA SYNTHETIC PATCH	6 MONTHS	NO	YES	NO	NORMAL	28	C	LOW	NO	YES	YES
F	60	CEA SYNTHETIC PATCH	3 MONTHS	NO	NO	NO	HIGH	26	A	LOW	NO	YES	YES
M	67	EVERSION	1 YEAR	NO	NO	NO	NORMAL	24	A	NORMAL	NO	YES	YES

Table 1. Baseline characteristics, demographics and risk factors

	EMBOLIC PROTECTION DEVICE	STENT	MANNITOL	HEMODYNAMIC DEPRESSION
1	NO	X-ACT (Abbott)8-6x40mm	NO	NO
2	NO	X-ACT (Abbott)8-6x40mm	YES	NO
3	NO	X-ACT (Abbott) 9-7x40mm	NO	NO
4	NO	X-ACT (Abbott) 8-6x40mm	NO	NO
5	YES (7.2 EMBOSHIELD NAV.)	X-ACT (Abbott) 9-7x40mm	NO	NO

Table 2. Periprocedural data

Figure 1. Initial angiogram showing the significant internal carotid artery stenosis

Figure 2. Final angiogram after the stenting of internal carotid artery showing the satisfying

RESULTS

We identified 196 patients treated for carotid artery disease. Five patients presented with carotid restenosis post CEA (2,5%). In our department, indication for revascularization procedure is (re)stenosis >80% (symptomatic/asymptomatic) or <80% in symptomatic patients in individuals with life expectancy more than 5 years. No plaque or other patient characteristics are taken into account for reintervention. In all cases, restenosis was asymptomatic, whereas only one patient was symptomatic in the first place (a major stroke was the indication for the CEA). The initial diagnosis was done with duplex scan in all patients. The majority of patients were women (60%), with low HDL levels (80%), increased BMI (60%) and high fibrinogen levels (60%). None of the patients required atropine administration intra or postoperatively. One patient required intravenous mannitol infusion postoperatively (50cc twice daily) because of mild hyper-perfusion syndrome (headache and confusion without neurological deficits). Moreover, all patients had normal postoperative levels of troponin.

All patients discharged the first postoperative day with double antiplatelet regimen and remain in surveillance protocol (1, 6 and 12 months and annually thereafter) which included physical examination, blood pressure measurement and duplex ultrasonography. Follow up ranges from 1 to 18 months and reveals primary patency in all cases.

DISCUSSION

Regarding pathophysiology, when restenosis occurs in the first month postoperatively, it is considered as residual atherosclerosis and not as restenosis. Restenosis generally begins 3 to 6 months postoperatively because of neointimal hyperplasia and after a time lapse of 2 years it is considered as recurrence of atherosclerosis.[1] According to the literature, the incidence of restenosis ranges from 3% to 30%[7]. Risk factors associated

with restenosis are diabetes mellitus, smoking, hypertension, female gender, small carotid diameter, renal failure, residual stenosis and primary closure of arteriotomy in the initial CEA[1,4,6,7]. Our observational study results suggests that female gender, hypertension, CEA using synthetic patch, low HDL levels, increased fibrinogen and increased BMI were common characteristics among patients with restenosis. Regarding the type of surgery, as in our department we rarely perform primary closure of arteriotomy following CEA, we cannot comment on the incidence of restenosis in this group of patients.

Management of restenosis remains debatable since restenosis is considered less aggressive than primary atherosclerosis. Symptomatic patients should definitely receive revascularization, but it is unclear whether asymptomatic patients are benefited from a repeated procedure. Considering treating strategy, both endovascular and open surgical repair has been described for this group of patients, especially if the patients present with symptoms. A recent metaanalysis suggests that CAS is not superior to re-do CEA concerning periprocedural stroke/death rates.[1,5] Nonetheless, patients treated with CAS have a lower risk for new restenosis and periprocedural cranial nerves injury.[5] Althogh cranial injury is considered transient and completely resolving within the first year, it remains a troublesome complication affecting the quality of life and limiting the benefit of carotid surgery. It is our belief that stenting is simpler and it could be preferred for several reasons. Firstly, re-do procedures are technically demanding because of the presence of fibrosis. Furthermore, CAS is associated with low risk for myocardial infarction. Another reason is patient's preference. It is a fact that re-do procedures brings discomfort to patients and their relatives, especially those with comorbidities. Moreover, since recurrence is usually caused by neointimal hyperplasia, protection device is not always mandatory. Though, in cases where residual lesion or recurrent atherosclerosis is suspected, one should anyhow use a protection device. Also, intra or postoperatively hemodynamic depression is unlikely to happen because carotid body is not functioning (due to dissection during the initial procedure). Finally, cost participates to some extent in decision making, especially in Greece. Hospital costs for CEA (operation plus four days of hospitalization) have the same hospital costs for CAS (stenting plus two days of hospitalization) which estimated to be approximately 1300 Euros. Concerning stent selection, surgeon's preference was a self-expanding, closed-cell, tapered, bare metal stent with high radial force in order to overcome rigid/calcified lesions. Nowadays, there is a variety of materials available in the market suitable for all anatomies and indications/contraindications of CAS in restenotic carotid ateries do not seem to differentiate from what we already know.

Based on our experience, CAS could be used to treat restenosis following CEA as it represents a fast, safe and effective solution. The small number of patients treated with this method is a limitation of this observational, retrospective study.

CONCLUSION

Individuals with restenosis following CEA can result to ipsilateral stroke. CAS combines several advantages (medical, aesthetic and social-economic) and it could be the preferred therapy for those patients. However, randomized control studies are essential to prove this suggestion.

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No conflict of interest.

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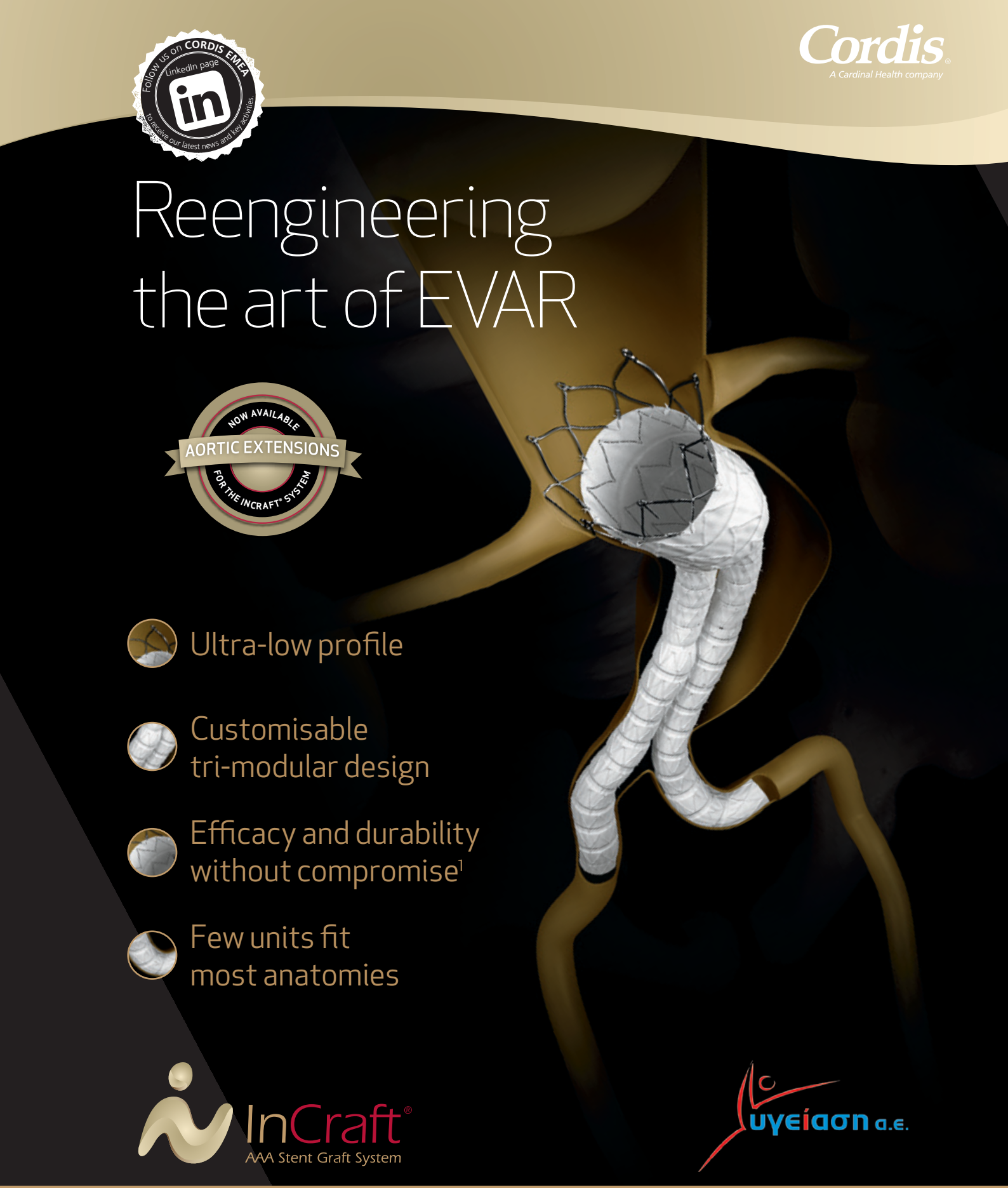

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Efficacy of micronized purified flavonoid fraction on postoperative symptoms after endovenous thermal ablation. A pilot randomized controlled study

Christos Karathanos, Konstantinos Mpatzalexis, Petroula Nana, Georgios Psaras, Konstantinos Spanos, Nikolaos Roussas, Miltiadis Matsagkas, Athanasios D. Giannoukas

Department of Vascular Surgery, University Hospital of Larissa, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

Abstract:

Objectives: Micronized purified flavonoid fraction (MPFF) is a venoactive agent with proven positive effects in the treatment of chronic venous disease. The aim of our study was to assess its clinical efficancy in the postoperative symptoms after endovenous thermal ablation (EVTA) associated with phlebectomies.

Methods: Patients undergoing endovenous thermal ablation [Laser (EVLA) or Radiofrequency (RFA)] of the greater saphenous vein associated with phlebectomies were randomized in those receiving MPFF agent 500mg Bid 7 days before and 30 days after the procedure (MPFF group) and in those who did not receive MPFF (Control group). Clinical classification (CEAP), 10-cm Visual Analog Scale (VAS) for pain, Venous Clinical Severity Score (VCSS) and Chronic Venous Insufficiency Quality-of-Life Questionnaire (CIVIQ) were recorded. Assesment visits were performed 7 days prior to ablation and 7 and 30 days post-ablation. Primary outcome was postoperative pain using the VAS scale and CIVIQ pain score. Secondary outcomes were improvement of VCSS and CIVIQ scores.

Results: 21 patients were randomized to the MPFF group and 21 in the control group. Patients' demographics, CEAP classification, type of ablation (EVLA or RFA), mean linear endovenous energy density, average vein diameter and length of ablated vein were comparable between the two groups. Mean preoperative VAS pain score and CIVIQ pain score were 5.7± 1.8 and 10.2± 3.7 in the MPFF and 5.7± 1.7 and 9.8± 3.8 in the control group while at 7-day post-operatively there was improvement in both groups (2.7± 1.1 VAS pain score and 6± 1.3 CIVIQ pain score in the MPFF vs. 3.5± 1.2 and 7.4± 2.2 in the control group, respectively), (p=.03). At 7–day postoperatively the MPFF group had better outcome compared to the control one in the CIVIQ pain score (from 10.2± 3.7 to 6± 1.3 vs. from 9.8± 3.8 to 7.4± 2.2) (p=.04). At 30-day post-operatively all patients showed a significant improvement in all domains compared to preoperative assessment (p=.02), but there were no differences between the two groups.

Conclusions: MPFF in patients undergoing endovenous thermal ablation may improve early postoperative pain. Larger studies are needed to confirm these findings.

Abbreviations: EVTA, endovenous thermal ablation; EVLA, enovenus laser ablation; RFA, radiofrequency ablation; CEAP, clinical-etiology-anatomy-pathophysiology; VAS, visual analog scale; VCSS, venous clinical severity score; CIVIQ, chronic venous insufficiency quality-of-life questionnaire.

INTRODUCTION

Chronic venous disease (CVD) is a common disorder reported to affect up to 60% of the general population.[1] The symptoms attributed to CVD varing to different degrees of severity including asympotomatic forms to disabiliting pain, heaviness and ulceration of the limbs affecting patients' quality of life (QoL).

Author for correspondence:

Christos Karathanos, MD, MSc, PhD

Department of Vascular Surgery, University Hospital of Larissa, Mezourlo, 41 110 Larissa, Greece
Tel/Fax: +30 2413501739,
E-mail: christoskarathanos@yahoo.gr
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The treatment options of patiets with CVD includes conservative treatment, traditional stripping surgery with ligation of the saphenofemoral juction (SFJ), endothermal thermal ablation (EVTA), mechanochemical ablation (MOCA), injection of cyanoacrylate glue and ultrasound guided foam sclerotherary.[2] Venoactive drugs (VADs) are considered an important component of the conservative treatment of CVDs, either alone or in combination with compression therapy.[2,3] Micronized purified flavonoid fraction (MPFF) is a venoactive agent with proven positive effects in the treatment of CVD, improving leg symptoms, edema and quality of life.[4] A recent study reported that, administration of VADs such as MPFF, may improve postoperative pain and hematoma in patients undergoing stripping surgery of the great saphenous vein (GSV).[5]

Current guidelines recommend EVTA techniques in preference to surgery, for the treatment of patients with GSV reflux (level of evidence A, class I).[2] The aim of our study was to as-

sess the clinical efficancy of MPFF in the postoperative symptoms after EVTA associated with phlebectomies.

MATERIALS AND METHODS

Patiets and Study Design

We conducted a single center, prospective, pilot randomized controlled study on patients undergoing EVTA at a tertiary center. Consecutive patients over 18 years of age with GSV incompetence confirmed by duplex ultrasound (DUS), clinical etiologic anatomic pathophysiologic classification (CEAP) clinical score C2 or more and anatomic criteria suitable for EVTA were eligible. Patients with deep vein incompetence, malignancy, recent surgery or trauma, pregnancy, lactation, deep vein thrombosis and/or pulmonary embolism within 6 months, systematic use of non steroid anti-inflammatory or other analgesics drugs, use of any venoactive drugs 30 days prior randomization or known allergy to the drug were excluded.

All patients underwent DUS of the superficial and deep veins of the lower limbs. Reflux was defined as retrograde flow during more than 0.5 s after calf compression.

Medical history, demographic characteristics, clinical examination defining the clinical class C of the CEAP classification, 10-cm Visual Analog Scale (VAS) for pain, Venous Clinical Severity Score (VCSS) and Chronic Venous Insufficiency Quality-of-Life Questionnaire (CIVIQ) were recorded.

After giving written informed consent, patients were randomly assigned in those receiving MPFF agent 500mg Bid 7 days before and 30 days after the procedure (MPFF group) and in those who did not receive MPFF (Control group). The randomization sequences were generated by a computerized random-number and distributed to each participant by the data coordinator in identical, sealed envelopes. Only patients that provided their consent to participate to the study, fulfilled our inclusion criteria and completed the follow up were included.

Procedures

We used the same procedural characteristics in both groups. EVTA was performed under local tumescent anaesthesia with a 1470-nm diode radial laser (EVLA) (Biolitec, East Longmeadow, Massachusetts) or radiofrequency (RFA) (ClosureFast™ Procedure, Medtronic, Mineapolis). The refluxing GSV was entered under DUS guidance and the tip of the fibre was positioned 1-2 cm from the SFJ. A perivenous tumescent anaesthesia was administered under DUS guidance in a fix solution consisting of 1000ml cold nature saline 0.9% with 50ml Xylocaine and 10ml sodium bicarbonate before EVTA. Laser was performed in the continuous mode at 10 W of power with a linear endovenous energy density of 80 J/cm. RFA was performed with a ClosureFAST device with a 7-cm heating element. Segmental energy delivery at 120°C was delivered in 20-second cycles. Two cycles were applied to the proximal vein, followed by one cycle to the remaining venous segments. Tributaries were removed by concomitant phlebectomies. At the end of all treatments, a compression bandage was applied. After 48 h, the bandage was replaced by a medical elastic compression stocking (ankle pressure 23-32mmHg) for 1 week during the day.

Outcome assessment and follow up protocol

Assesment visits were performed 7 days prior to ablation and 7 and 30 days post-ablation. Postprocedural DUS was performed to assess the status of vein occlusion and thrombosis. Any adverse events were also recorded. Patients were asked to complete a questionnaire at each visit that focused on pain assessment using a validated visual analog scale ranging from 0 (no pain) to 10 (most severe pain) (VAS score) and a validated CIVIQ score. All aspects (clinical, physical, social and psychological) of the CIVIQ score were recorded and analyzed. Primary outcome was postoperative pain using the VAS scale and CIVIQ pain score. Secondary outcomes were improvement of VCSS and CIVIQ scores.

STATISTICAL ANALYSIS

The relationships of categorical variables and the main outcomes observed (pain cores, CIVIQ, VCSS) were examined with the use of the x^2 statistic, whereas the relationships between main outcomes and continuous measurements were assessed with the independent samples t test or the Mann-Whitney test, where appropriate. For the change in the CIVIQ measures, the paired samples t test was applied for each of the dimensions measured.

RESULTS

Between September 2017 and March 2018 we randomly allocated 21 eligible patients to the MPFF group and 21 to the control group. Table 1 shows the main characteristics of the study population. There were no significant differences between the groups regarding demographics and clinical characteristics. The majority of the patients (86%) were C2 - C3 CEAP clinical class. Preoperative clinical scores including VAS, VCSS and CIVIQ were not different between the two groups (table 2).

	MPFF group	CONTROL group
No	21	21
Female	9	13
Age (mean), (min-max)	52 (33-70)	53 (33-80)
Limb Right	10	10
CEAP 2,3	18	18
CEAP 4,5,6	3	3

Table 1. Study population characteristics
Abbreviations: CEAP, clinical-etiology-anatomy-pathophysiology

Twenty patients underwent RFA and 22 EVLA. Limbs treated with EVLA received a mean linear endovenous energy density of 83 ± 5.6 J/cm. Mean maximum vein diameter measured 15cm below SFJ and mean length of treated segment were comparable between 2 groups (16 ± 3.4 vs 17± 4.2 and 32±3 vs 35± 5, respectively). The amount of tumescent anaesthesia used was 450ml ± 80 in MPFF group and 470ml ± 60 in the control group (p=.89).

	MPFF group	CONTROL group	P Value
VAS	5.7 ±2.1	1.3 ±1	.785
VCSS	5.8 ±2.6	5.8 ±2.8	.962
CIVIQ Global	37.5±11.3	40.8±15.4	.403
CIVIQ Pain	9.7±3.7	10.2±3.8	.655
CIVIQ Physical	7.2±3.3	7.9±3.8	.556
CIVIQ Social	5.1± 2.4	5.9±2.5	.322
CIVIQ Psychological	15.2±4.5	17.1±7.3	.325

Table 2. Preoperative characteristics of the patients
Abbreviations: VAS, visual analog scale; VCSS, venous clinical severity score; CIVIQ, chronic venous insufficiency quality-of-life questionnaire
Note.-Values expressed as means ±SD.

Primary outcomes

As illustrated in Fig 1 both groups improved the VAS pain score 7 days after the intervention in comparison to baseline (5.7± 1.8 vs 2.7± 1.1 in MPFFgroup and 5.7± 1.7 vs 3.5± 1.2 in control group) and kept improving it 30 days postoperatively (1.1± 0.4in MPFFgroup and 1.5± 0.6in control group) but without any statistical difference. At 7-day postoperatively the MPFF group had better outcome compared to the control one in the CIVIQ pain score (from 10.2± 3.7 to 6± 1.3 vs. from 9.8± 3.8 to 7.4± 2.2) (p=.04) (Fig 2). This statistical difference was not sustained at 30-day postoperatively as both groups showed a significant improvement in the CIVIQ pain score compared to preoperative assessment (4.8± 1.6 vs 5.2± 1.2) (p=.02) (table3).

	Preoperative	30-days Postoperative	P Value
VAS	5.7 ±3.2	2.7 ±2.2	.032
VCSS	5.8 ±2.6	5.8 ±2.8	.039
CIVIQ Global	39±13.5	24.5±4.8	.038
CIVIQ Pain	10±3.7	5±1.4	.022
CIVIQ Physical	7.5±3.5	4.8±1.2	.033
CIVIQ Social	5.5± 2.5	3.7±1.1	.042
CIVIQ Psychological	16.2±6	11.2±2.4	.045

Table 3. QOL scores changes of study population
Abbreviations: QOL, quality of live; VAS, visual analog scale; VCSS, venous clinical severity score; CIVIQ, chronic venous insufficiency quality-of-life questionnaire
Note.-Values expressed as means ±SD.

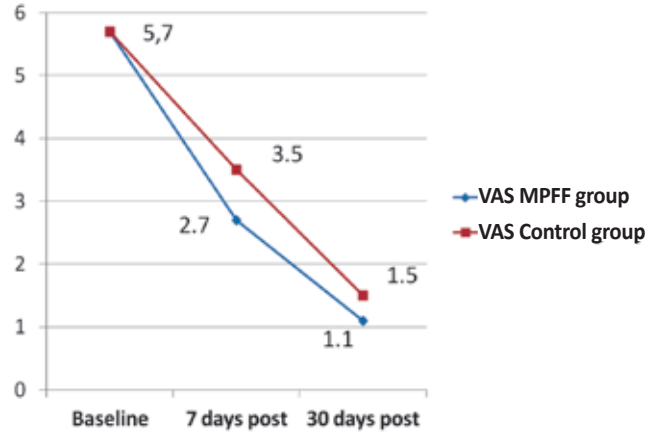

Figure 1. Changes in VAS score

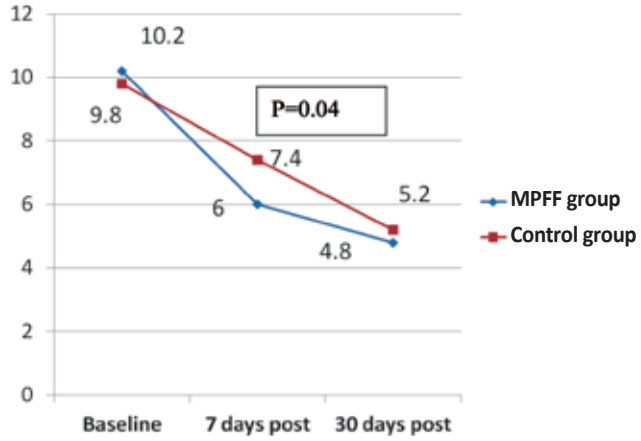

Figure 2. Changes in CIVIQ pain score

Secondary outcomes

There were no significant differences in VCSSs between treatment groups preoperatively (5.8± 2.8 in MPFF group vs 5.8± 2.6 in control group, p=.96). At 30-day postoperatively all patients showed a significant improvement in VCSS (2.0± 2.1 vs 2.1± 2.4, respectively), although non- significant between the two groups (p=.94).

CIVIQ scores between treatment groups at randomization were comparable (p=.403) (table2). As it demonstrates in table 3 there was a significant improvement in all patients in global and also in all domains of CIVIQ score 30 days after treatment but there were no significant differences between the two groups (table 4). GSV occlusion was achieved in all cases and no advesre events related to the procedure such as thrombosis were observed.

	MPFF group	CONTROL group	P Value
VCSS	2±2.1	2.1±2.4	.945
VAS	1.1± 0.8	1.5± 0.7	.104
CIVIQ Global	23.6±4	25.3 ± 5.4	.240
CIVIQ Pain	4.9±1.7	5.2± 1.2	.455
CIVIQ Physical	4.5± 0.9	5± 1.4	.167
CIVIQ Social	3.4± 0.9	4± 1.2	.089
CIVIQ Psychological	10.8± 2	11.7±2.8	.233

Table 4. QOL scores measurements at 30 days postoperative
Abbreviations: QOL, quality of live; VAS, visual analog scale; VCSS, venous clinical severity score; CIVIQ, chronic venous insufficiency quality-of-life questionnaire
Note.-Values expressed as means ±SD.

DISCUSSION

The current study focused on early postoperative recovery period differences between patients receiving MPFF after EVTA in a prospective, randomized manner. The trial demonstrates the early favourable clinical outcomes and QoL improvement following EVTA, with significant improvement in postoperative pain in patients receiving MPFF.

MPFF is an established VAD, and its marketed formulation (Daflon®) is a flavonoid based venoactive drug containing 90% of micronized diosmin and 10% of other active flavonoids (di-

osmetin, hesperidin, linarin and isorhoifolin).[4] Diosmin acts on microcirculation by reducing the capillary hyperpermeability and fibrinolysis, increases the frequency and the intensity of the venous contractions, improves venous tone and reduces venous stasis.[6] In a randomized, double-blind, placebo-controlled parallel-design trial using VAD, there was a significant improvement in QoL and also in limb edema and pain/ burning sensation in the aminaphthone and MPFF groups.[6] A recent meta-analysis by Kakkos et al,[4] reported that MPFF is high effective in improving leg symptoms, edema and quality of life in patients with CVD. The effect of MPFF in the postoperative period in patients undergoing convesional surgery has also been studied. Vervekova et al,[5] showed that patients receiving Daflon 500mg Bid 14 days prior to and 14 days after surgery had smaller hematoma, lower postoperative pain and a lower consumption of analgesics. A recent multicenter study by Bogachev et al,[7] reported that administration of MPFF agent in patients undergoing phlebosclerosing procedures for reticular veins and telangiectasias showed greater improvement in venous symptoms and QoL scores and also reduced the occurrence of post injection hyperpigmentation compared to sclerotherapy alone.

In the recent years EVTA have become very popular in the treatment of saphenous vein incompetence, as a minimally invasive procedure alternative to classical surgery (high ligation and stripping). The two most frequently used techniques are EVLA and RFA.[2] In our study clinical and procedural characteristics between MPFF and control group were comparable. In addition, all patients underwent a concomitant plebectomies. The amount of tumescent anaesthesia used was not different between the two groups. In order to avoid any potential bias of tumescent anaesthesia used assessment visits were performed at 7 and 30 days post ablation. Both groups improved VAS pain score, CIVIQ and VCSS at 7 and 30 days postoperatively without any statistical difference. A subgroup analysis of all aspects of CIVIQ score showed a significant improvement in the CIVIQ pain score at 7 days in the MPFF group compared to the control. The administration of MPFF in these patients seems to improve postoperative pain. This can result in lower consumption of analgesics, quicker recovery and faster return to normal activities.

Comparing EVLA with RFA, our study shows equal levels of postoperative pain. Others reported that, patients treated with RFA have less postoperative pain and bruising compared with EVLA.[8-11] However, in these trials the ClosureFast catheter was compared with lower wavelength lasers using a bare fibre. Arslan et al [12] compared 980 nm versus 1470 nm wavelength, and it was demonstrated that 1470 nm diode laser had a significant reduction in pain levels, ecchymosis, paraesthesia and induration. The 1470 nm wavelength radial-tip fiber system enables the procedure to be done at lower energy levels with lower side effect incidence. Another possible explanation for comparable postoperative pain between EVLA and RFA is the usage of MPFF agent.

Numerous studies have showed that, patients treated with EVTA reports less postoperative pain compared to patients treated with convesional surgery.[13-16] One such study compared the results of conventional surgery done under tumescent local anesthesia with EVLA, RFA and foam sclerotherapy[14]. The results showed that the postoperative average pain scores at 10 days was significantly lower in the groups treated with RFA and foam sclerotherapy comparing to surgery and EVLA, however the VCSS, QOL scores and efficiency at 3 years were not significantly different between all treatment modalities. Venermo et al[16] reported that, perioperative pain was significantly reduced and the duration of sick leave was shorter after EVLA (8 days) than after surgery (12 days).

In our study occlusion rates 30-day postoperative was 100% in both techniques. In numerous studies EVLA and RFA shows comparable occlusion rates.[8-11] Weiss et al,[17] published a retrospective comparison of three different EVTA systems. At 5-year follow-up, successful ablation rates of RFA, 810 nm, and 1,320nm wavelengths were 61.7%, 65.7%, and 84.7%, respectively. In our study we used the 1470 nm diode radial laser (EVLA) (Biolitec, East Longmeadow, Massachusetts) and the ClosureFast™ Procedure catheter (RFA), (Medtronic, Mineapolis). Up to now no comparative trials have been published comparing the use of these two ablation systems.

This study has some limitations. It is a pilot study with small number of patients. Most of the patients included to the study were categorized to C2,3 severity of venous disease according to CEAP classification. Therefore, the number of the patients with severe disease was relatively small to allow consistent comparisons with the group of patients with moderate disease. The small number of patients did not allowed us to make comparison between different EVTA techniques and the role of MPFF agent in the early postoperative period. The possibility of bias was minimized by the use of validated QOL scores patient-reported outcomes, and objective criteria and ultrasound protocols were used in the assessment of researcher-reported outcomes. Another potential limitation is that patients in the control group did not receive any medication similar to the MPFF group and there is a chance for reporting bias as we have conduct a pain severity and QoL scores study.

CONCLUSION

Patients with CVD treated with EVTA significantly improve both clinical and physical aspects during early postoperative period. The administration of MPFFagent may improve early postoperative pain. Larger studies are needed to confirm these findings.

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Applied statistics in vascular surgery Part III: Understanding Analysis of Variance (ANOVA) and its subtypes

Constantine N. Antonopoulos[1], Efthymios D. Avgerinos[2], Larry Fish[3], John Kakisis[1]

[1]Department of Vascular Surgery, Athens University Medical School, "Attikon" Hospital, Athens, Greece
[2]Department of Vascular Surgery, University of Pittsburgh, UPMC Presbyterian Hospital, Pittsburgh, PA
[3]Department of Surgery, University of Pittsburgh, UPMC Presbyterian Hospital, Pittsburgh, PA

Abstract:

Statistical testing is rather simple in the case of a continuous dependent variable and one independent two-group variable; the t-test will determine whether the two means differ significantly from each another. However, when the independent variable has more than two independent levels, then further t-test calculations potentially introduce a type I error. The one-way analysis of variance (ANOVA) will test for differences among three or more groups while controlling experiment-wise type I error. A subsequent multiple comparison (post-hoc) test will identify pairs of groups that are significantly different. The ANOVA can be used in several research designs, such as repeated-measures (or within-subjects), mixed-model (or within-between), factorial (or two-way, three-way ANOVA etc), analysis of covariance (ANCOVA) and multivariate analysis of variance (MANOVA), after taking into consideration the levels of the independent variable and its covariates.

INTRODUCTION

A student was asked to compare maximum aortic diameter in patients with abdominal aortic aneurysm (AAA) at the end of the first month after open surgical repair (OSR; group A) and endovascular aortic repair (EVAR; group B). The null hypothesis is that the mean maximum aortic diameter after OSR is the same compared to EVAR. The statistical testing looks rather straightforward; there is one continuous dependent variable (maximum aortic diameter) and one independent variable (type of AAA repair) with two independent groups (OSR and EVAR). The student will compute mean maximum aortic diameter for OSR and EVAR and then the *independent samples t-test* will examine whether the two means greatly differ from each other[1].

When, however, we want to test for maximum aortic diameter differences among patients treated with seven different endografts at the end of the first month after EVAR, analysis might be more complicated. In that case, there would be 21 different comparisons and thus we would need to perform 21 different t-tests simultaneously (Supplemental Material). However, for each individual t-test, the probability of type I error would be 5% and "experiment-wise" the probability of type I error, across all pair-wise comparisons, would be higher. To avoid inflating the experiment-wise probability of type I error when we compare more than two means, we should use *Analysis of Variance (ANOVA),* which provides only one overall test; a test of whether all the population means are equal[2]. The t-test is a type of ANOVA dealing with one continuous dependent variable and one independent variable with two groups. In our second scenario, ANOVA is the method of choice, as we have one continuous dependent variable (maximum aortic diameter) and one independent variable (type of endograft used) with seven groups (seven different types of endograft).

Author for correspondence:

Constantine N. Antonopoulos

Department of Vascular Surgery, Athens University Medical School, Attikon University Hospital, Athens, Greece
E-mail: kostas.antonopoulos@gmail.com
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BASIC CONCEPTS OF ANOVA

The one-way ANOVA is used to test for differences among the levels of an independent variable, with respect to the mean value of the independent variable, also called a factor. ANOVA is used as a test for comparison between means, but it uses variance as a tool for evaluating the sizes of those mean differences. As a result, intragroup and intergroup variability is what is actually being analysed in ANOVA. A main result of the ANOVA model is the F statistic (also called the F-ratio), The formula, which conveys the general concept behind the F-ratio, is: *F-ratio = Between-groups variance / Within-groups variance*. The formula for F varies among models, and even within models. If no differences are found among the tested groups - the null hypothesis -the F-ratio will be close to 1[3].

BASIC ASSUMPTIONS OF ANOVA

ANOVA controls for multiple type I errors and thus maintains the experiment-wise alpha level at the desired value (usually 0.05). To be valid, the ANOVA requires that two assumptions be satisfied: a) The dependent variable (eg. maximum aortic diameter) must be normally distributed in each of the populations being compared (eg. in each group of the 7 different

endografts used), b) The variance of the dependent variable is constant among the populations being compared (eg. the 7 groups of different endografts used)[3]. If the first assumption is violated, the researcher should perform data transformation or perform nonparametric *Kruskal-Wallis H Test*, while if the second assumption is violated, other tests like *Welch* of *Brown and Forsythe* can be used[3]. Certain ANOVA models, to be discussed below, may require additional assumptions.

OTHER ANOVA MODELS

As reported in the previous section, when dealing with one continuous dependent and one independent variable with multiple groups we should use one-way ANOVA (Table 1). If, however, the dependent variable was measured on multiple occasions (or under different conditions), but on the same subjects, *repeated-measures (or within-subjects) ANOVA* is used. In this model the levels of the independent variable will represent the occasions, or the circumstances, in which each subject was observed. When examining differences in the continuous dependent variable both by groups and time, then a *mixed-model (or within-between) ANOVA* should be used. In the case of one continuous dependent and two or more independent variables, the appropriate test is *factorial ANOVA (or two-way, three-way ANOVA etc)*[2,4].

If we want to examine differences in a continuous dependent variable between groups of an independent variable (ANOVA), but we need to control for potential confounders, the analysis is called *analysis of covariance (ANCOVA)*. ANCOVA can be applied to a between-subjects design, a within-subjects design, or a mixed-model design. Finally, when the model incorporates multiple continuous dependent variables, then a multivariate analysis of variance (MANOVA) is used to investigate differences among the levels of the independent variables, with respect to their effects on a composite of the dependent variables. *Multivariate analysis of covariance* (MANCOVA) is the extension of MANOVA to incorporate control for potential confounders[2,4].

		Dependent Variable(s)	
		1 (eg. maximum aortic diameter)	**≥2** (eg. maximum aortic diameter and aortic neck length)
Independent Variable(s)	**1** **with 1 group** (eg. all patients with AAA)	One sample t-test	-
	1 **with 2 groups** (eg. patients after EVAR and patients after OSR)	Independent samples t-test	Hotelling's t-test
	1 **with ≥3 groups** (eg. patients treated with 7 types of endograft)	one-way ANOVA	one-way MANOVA
	1 **measured multiple times over time or under different conditions but on the same subjects** (eg. same patients with AAA, with post-treatment follow-up measures for each patient post EVAR	**2** **measurements** **per subject** Dependent samples t-test **≥3** **measurements** **per subject** repeated-measures ANOVA	repeated-measures MANOVA
	1 **with control for potential confounders** (eg. type of operation, controlled for age)	ANCOVA	MANCOVA
	≥2 (eg. type of operation and age-group)	factorial ANOVA (two-way, three-way ANOVA etc).	factorial MANOVA (two-way, three-way MANOVA etc).

Abbreviations: AAA: abdominal aortic aneurysm, EVAR: endovascular aortic repair, OSR; open surgical repair, ANOVA: analysis of variance, ANCOVA: analysis of covariance (ANCOVA), MANOVA: multiple analysis of variance MANCOVA: multiple analysis of covariance

Table 1. Types of suggested analysis according to the number of dependent, number and type of independent and groups of independent variable(s)

POST-HOC TESTING

Although ANOVA tests for differences among groups of an independent variable, it cannot tell us which particular group means differed from each other. If we want to determine which particular group means differed from each other, a *post hoc test* is usually required. There are several post-hoc tests available and the choice depends on the form of the post-hoc hypothesis being tested, or on how badly the homogeneity of variance assumption has been violated. Among them, when equal variances are assumed, available multiple post-hoc tests are Bonferroni, Tukey's honestly significant difference test, Sidak, Gabriel, Hochberg, Dunnett, Scheffé, and LSD (least significant difference). When equal variances are not assumed, the appropriate post-hoc tests, which may be more robust, include Tamhane's T2, Dunnett's T3, Games-Howell, and Dunnett's C[5].

A special assumption, called sphericity, must be satisfied in repeated-measures ANOVA; the assumption is that the variances of the differences between all possible group pairs are equal. When Mauchly's Test of Sphericity indicates that data violates this assumption, corrections like the lower-bound estimate, Greenhouse-Geisser and Huynh-Feldt adjustments are applied to the degrees of freedom in the F-ratio in order to avoid increases in the type I error rate[3].

CONCLUSION

One-way ANOVA is a statistical model, which tests the hypothesis that the means of a dependent measure differ among two or more populations. When a significant F-ratio is found, a multiple comparison (post-hoc) test may be used in order to identify which of the three or more groups are different. This, and other models of ANOVA, such as repeated-measures (or within-subjects), mixed-model (or within-between), factorial (or two-way, three-way ANOVA etc), ANCOVA and MANOVA can be used appropriately after taking into consideration the levels of the independent variable and its covariates.

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Supplemental Material

In case of (**n**) groups, the number of possible comparisons (**C**) among them is given by the formula: **C= [n* (n-1)]/2**. For n=7 groups (7 different types of endograft) we get: C=[7*(7-1)]/2 = 21.

https://www.dcode.fr/combinations

Analysis of the Greek Vascular Surgical Trainees' appreciation of e-Learning

Vassilios Zymvragoudakis[1, 2], Sean Matheiken[3, 4], Nikolaos Patelis[1, 4, 5]

[1]European Vascular Surgeons in Training (EVST), Bordeaux, France
[2]Guy's & St Thomas' NHS Foundation Trust, London SE1 7EH, UK - EU
[3]Bedford Hospital, MK42 9DJ, UK - EU
[4]European Society for Vascular Surgery e-Learning
[5]Athens Medical Center, Marousi 15125, Athens - Greece

Abstract:

Introduction: e-Learning (e-L) offers great market value and manifests an exponentially increasing global annual growth rate. Despite this growing demand for e-L material, the medical field appears to be left behind. The aim of this study is to examine the current role and potential future of e-L in the field of vascular surgery in Greece, as evaluated by the Greek vascular surgeons in training.

Materials & Methods: A questionnaire in Greek was prepared and emailed to all Greek vascular surgery trainees. The questionnaire was anonymized although participants were encouraged to share their details.

Results: Twenty trainees out of 35 (57.1%) participated in the survey. Participants demonstrated basic knowledge of what is e-L (85%), its advantages and disadvantages, and how e-L is delivered. Despite mediocre or non-existent prior experience to e-L, participants also reported that the future role of e-L is very important during or after the completion of their training in combination with traditional training. According to the surveyed trainees, the main advantages of vascular e-L are that it is available online for indefinite time (90%); it is not limited by geography (85%); no commuting is necessary (75%); and additional educational material is available through the course (65%). 45% believed that the major disadvantage of e-L is the isolation from the trainer while another 20% considered isolation from fellow trainees to be most important.

Conclusions: e-L for Greek vascular surgeons is still in its nascence, demonstrating both the great promise and the unsolved problems inherent in the early phase of a technology's growth. Greek trainees believe in the importance of the future role of e-L in their training.

INTRODUCTION

e-Learning (e-L) and m-Learning (m-L) are two terms increasingly used in all aspects of education, training and continuous professional development. e-Learning is the vocational education or training achieved by electronic means, while m-Learning represents learning across multiple contexts using personal electronic devices.[1] These educational tools are distinct parts of Technology Enhanced Learning (TEL) as they both employ electronic means to provide education or training.[2] e-L offers great market value and manifests an exponentially increasing annual growth rate. Despite the growing global demand for e-L material, the medical field appears to be left behind, particularly in certain specialties and countries, although some examples of successful e-L programs are currently available in some specialties.[3-5]

The aim of this study is to examine the current role and potential future of e-L in the field of vascular surgery in Greece, as evaluated by the Greek vascular surgeons in training.

Author for correspondence:

Dr Nikolaos Patelis, MD, MSc, PhD

Vascular Surgeon, Athens Mecial Center, Kifisias 56, Marousi 15125, Athens - Greece
Tel: +30 6993472472
E-mail: info@nikolaospatelis.gr
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METHODS AND MATERIALS

A questionnaire in Greek was prepared by the two authors (Supplementary material #1 and #2). The questionnaire consisted of 19 questions divided in the following sections:

- Understanding of basic terms on e-L (Questions 1-2)
- Prior experience with e-L (Questions 3-8)
- Future views regarding e-L (Questions 9-13 and 18)
- Views regarding the organization of future e-L (Questions 14-17)
- Feasibility of learning a technical skill online (Question 19)

The link to the questionnaire was hosted using the online free service of Google Forms (Google LLC, USA).

The questionnaire was emailed to 35 vascular surgeons in training at all the Greek hospitals recognized as training centers. It was available online for a period of three weeks.

The deadline for answering the questionnaire was March 13th, 2019. Anonymization was permitted as default, although trainees were encouraged to share their email address in order to receive their replies as well as the results of this online survey.

As per European Vascular Surgeons in Training (EVST) byelaws, trainees over the age of 40 and those who have completed their training but had not attempted the national board exam were excluded from the mailing list.

RESULTS

Understanding of basic terms on e-L

Twenty trainees (57.1%) participated in the survey by submitting the form. The majority of them (85%) answered that e-L is "*vocational education or training achieved by electronic means (mainly via the Internet)*", while 15% answered that e-L is "*vocational education, training or training achieved delivered exclusively via the Internet*".

In the question what constitutes e-L, all trainees (100%) replied online lessons, 35% answered lessons using a simulator, and 5% answered lessons in a classroom. Almost all trainees (n=19, 95%) thought that asynchronous lessons are part of e-L and 75% that synchronous lessons are part of e-L.

Prior experience with e-L

Approximately two thirds of the trainees (60%) did not have prior experience with e-L and 90% did not have any prior experience with vascular surgery e-L.

On a scale from 1 (totally satisfactory) to 5 (totally disappointing), both prior experience with general and vascular surgery e-L received an average score of 2.5 (Figures 1 & 2). Eight people had prior experience with e-L in general, while only two had vascular surgery e-L experience.

Two thirds (65%) were aware that foreign educational institutions run e-L courses that lead to an official qualification in the form of a certificate or diploma.

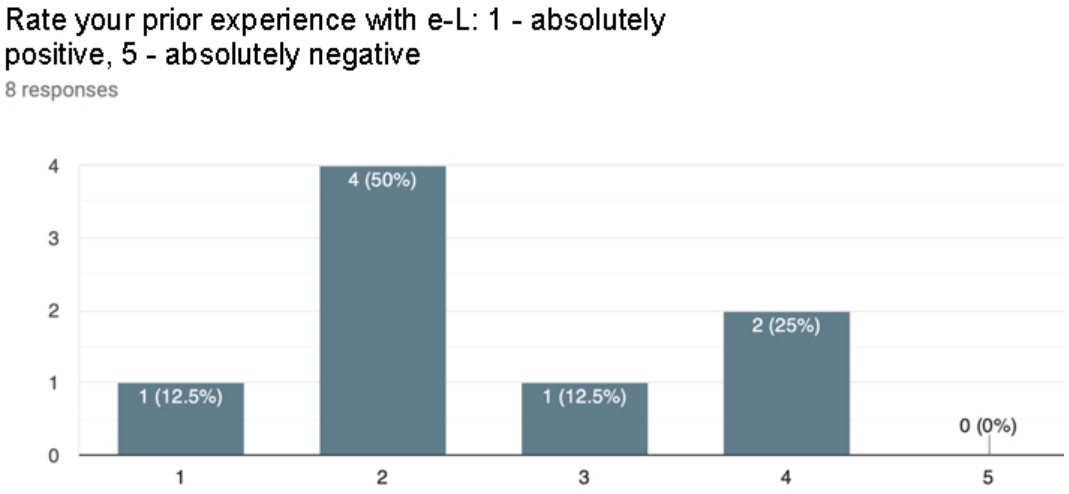

Figure 1. Ratings of previous e-L experience; 1 - absolutely positive, 5- absolutely negative

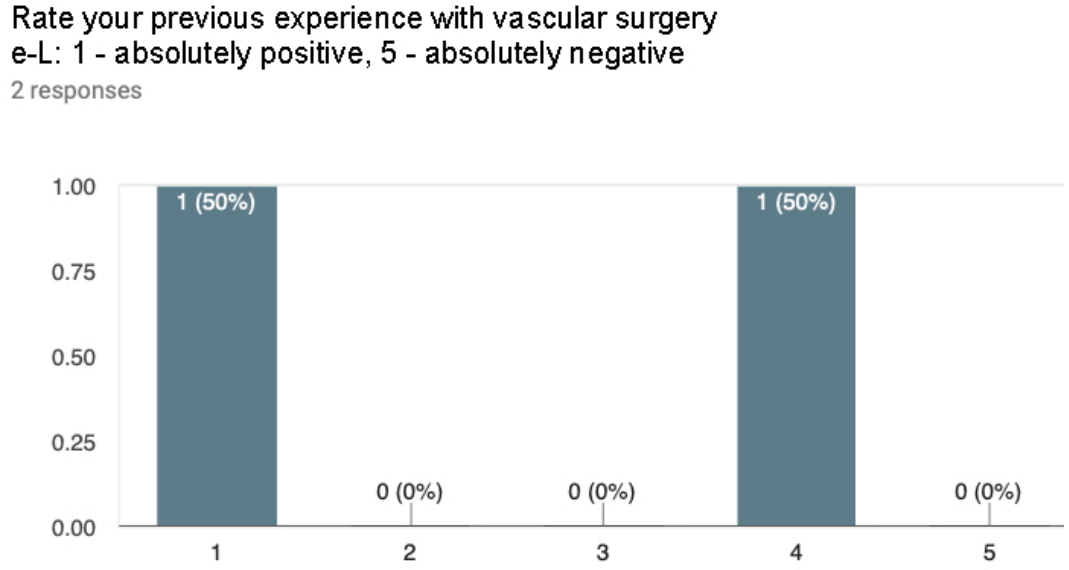

Figure 2. Ratings of previous vascular surgery e-L experience; 1 - absolutely positive, 5- absolutely negative

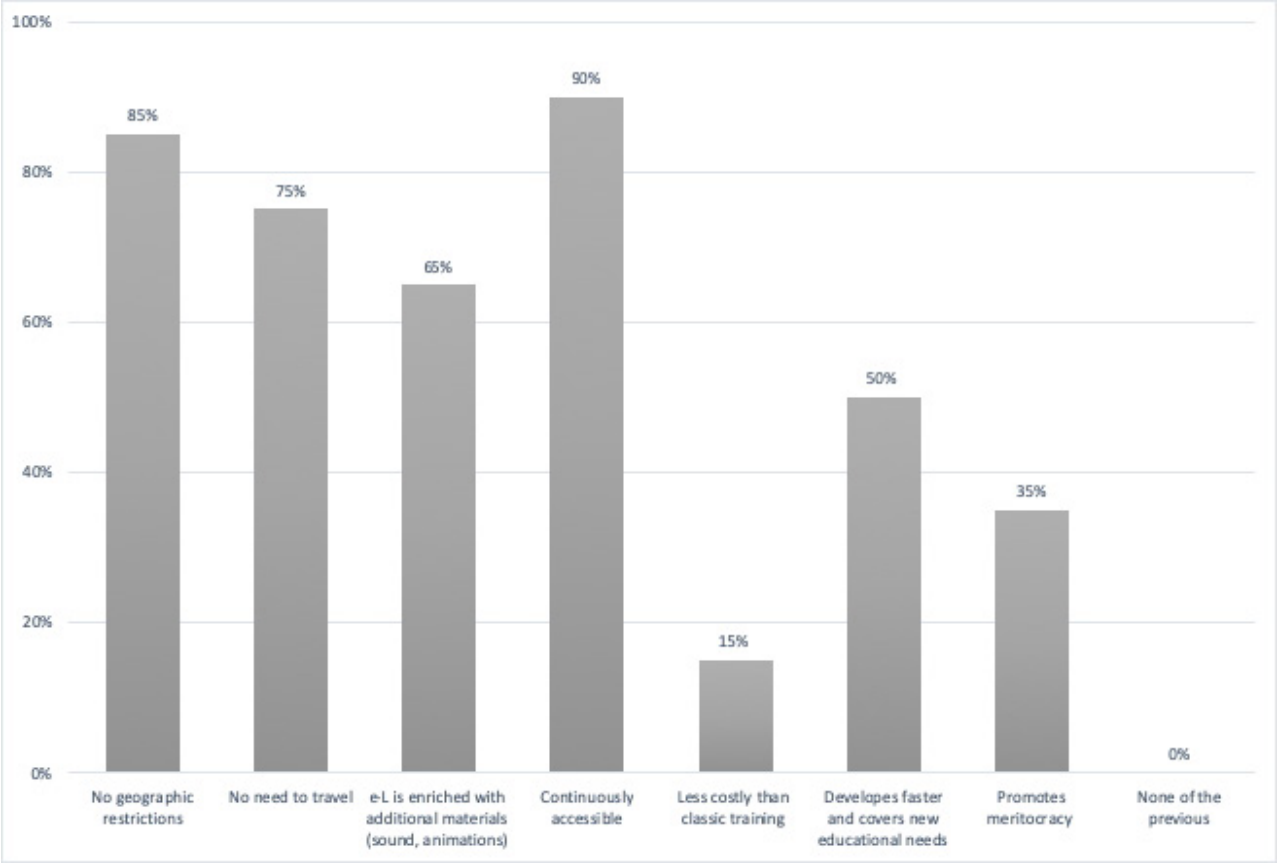

Figure 3. Advantages of e-L

Future views regarding e-L

All trainees (100%) believed that there is a place for e-L in future vascular surgery training.

According to the trainees, the main advantages of vascular e-L are that it is available online for indefinite time (90%); it is not limited by geography (85%); no commuting is necessary (75%); and additional educational material is available through the course (65%) (Figure 3).

Approximately half of the trainees (45%) believed that the major disadvantage of e-L is the isolation from the trainer while another 20% considered isolation from fellow trainees to be the most important disadvantage (Figure 4).

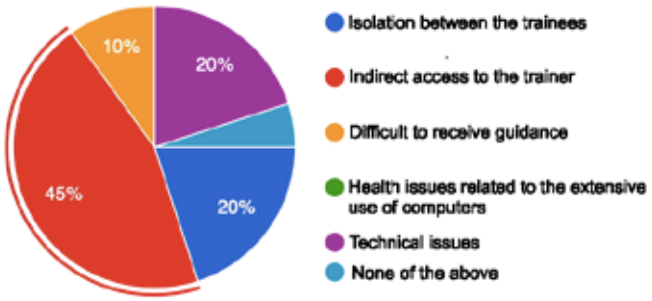

Figure 4. Disadvantages of e-L

All trainees (100%) believed that vascular surgery e-L would benefit both the surgeons in training and the post-training vascular surgeons.

Depending on the subject to be taught, all trainees (100%) favored the use of classical training and e-L in combination as their ideal learning modality.

Views regarding the organization of future e-L

All trainees desired that the vascular community should invest in developing an e-L program and 70% considered that this program should be developed by the surgical societies (Figure 5).

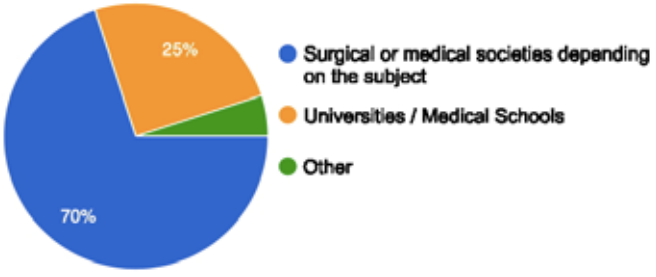

Figure 5. Who should develop a vascular surgery e-L project?

Regarding the financial burden of developing an e-L program for vascular surgeons and surgeons in training, opinions were divided (Figure 6). One third (35%) of the trainees believed that trainees should have access for free while post-training colleagues should pay a fee. Approximately the same percentage of trainees (30%) considered that the development should be financed by private companies that will advertise their products in adherence with the ethical guidelines for medical advertisement.

Figure 6. Who should cover the cost of an e-L project?

All trainees (100%) believed that e-L will play a significant role in vascular surgery in the future.

Feasibility of learning a technical skill online

Finally, 70% of the trainees considered it feasible to learn a practical skill online, while 25% agreed that it is feasible only for carefully selected subjects.

DISCUSSION

TEL consists of e-L, m-L, simulator-based training and the latest addition, cloud-based learning or c-L.[6] Despite all of the above terms being increasingly utilized in medical and surgical specialties, the most frequent term that physicians know is e-L. It is not surprising that employees in all fields, including healthcare providers, are becoming more familiar with e-L. The global expenditure for e-L projects reached USD 51.5 billion in 2016; this field has been growing by a steady annual rate of 7.9% since 2012.[7] This progress in e-L consumption is led mainly by less developed countries.[7]

The aim of this study is to examine the current role and potential future of e-L in the field of vascular surgery in Greece, as evaluated by the Greek vascular surgeons in training. The number of vascular surgeons in training in Greece is 35, rather low compared to larger first world countries, with mixed impact upon this study. A benefit of this limited population is obtaining questionnaire responses from twenty participants (57.1%) provides a sample size large enough to provide valid data representing the whole group of trainees. On the other hand, the limited number of participants negatively affects our ability to apply definitive conclusions to any larger cohort of trainees (e.g. all EVST members). The latter statement is further affected by the fact that this study is limited to Greece, a country superior only to Romania amongst the European Union (EU) countries based on the 2018 Digital Economy and Society Index (DESI).[8] Despite the comparably high expenditure of Greece on educational institutions of all levels, this country seems to spend less on e-L than other EU countries with similar characteristics, e.g. Slovakia or Estonia, two other small EU countries with their distinct languages and a significant rate of growth in their TEL sector.[7] Therefore, the size of Greece and the small number of Greek speakers - compared to e.g. English or German - may not be the reasons behind the lack of a significant e-L investment and growth. Of course, Greek vascular surgeons and trainees are a very small group within a small country and the limited number of potential users of a dedicated vascular e-L program makes the initial investment cost-prohibitive. Possible solutions to reduce the financial burden of building a vascular e-L project would be to either build e-L materials that could be reemployed without any or with a few changes, or host the vascular e-L project within a larger institution or company that manages a significant number of other e-L programs splitting costs between all users. Although the overall efficacy and effectiveness of e-L are already well established, the related cost-effectiveness is still under debate and should be further supported by further evidence.[9]

Although a number of different definitions for e-L exist, a widely accepted definition is *"vocational education or training achieved by electronic means (mainly via the Internet)"*. The majority of participants chose this definition as the right one, while the remainder chose a slightly narrower definition- *"vocational education, training or training achieved delivered exclusively via the Internet"*. Therefore, all the participants recognized what e-L is, a positive finding as it demonstrates that all participants possessed the most basic knowledge regarding e-L. It should be noted the e-L is not only provided via the internet but it can also be provided through a local network (e.g. workplace or hospital) or a dedicated wider network (e.g. university).

e-L can be provided in an asynchronous or synchronous format. Asynchronous learning occurs when the trainer produces and trainees attend at different time points (e.g. online video course continuously available), while synchronous is when the trainer produces and trainees attend simultaneously (e.g. live video class). Most of the participants answered that asynchronous and synchronous are both formats of e-L (95% and 75%, respectively). Therefore, participants are aware of the two different formats. All participants correctly chose that online courses are examples of e-L. A third of them (35%) considered simulator-based training as part of e-L, which is not the case, although simulators are part of TEL. Only one participant considered that lessons in a class are an example of e-L, something that could be true if an electronic method of delivering the material was used. An example of that would be a recorded video lecture delivered through the internet to a remote class while the trainer accepts questions from the trainees in a live chat feed.

Many of the participants did not have a previous experience of e-L (60%) and almost all of them (90%) did not have any previous experience with vascular surgery e-L. These results came to the authors' surprise, as the European Society for Vascular Surgery (ESVS) was the first to build e-L materials aiming in the education and training of both specialists and trainees.[6,10] Apart from ESVS, other platforms also exist and provide e-L materials to vascular surgeons and trainees. The fact that Greek trainees did not participate to any e-L activity

could be the result of a language barrier and/or poor advertising of the e-L courses in Greece. Two thirds (65%) of the Greek trainees knew that respected foreign academic institutions offer e-L courses leading to certified qualifications, therefore advertising could be considered sufficient regarding other fields, but not regarding vascular surgery. The underlying reasons behind these findings should be further examined. Participants who had e-L experience, rated their prior general and vascular learning as mediocre (score 2.5).

All participants considered that there is a place for e-L in vascular surgery. Participants recognized the benefits of e-L to be the absence of geographical restrictions (85%); elimination of the need for travel (75%); the ready availability of further educational material (65%); the constant accessibility of asynchronous e-L (90%); and the promotion of meritocracy as e-L training materials and assessment are not training center-dependent. These advantages of e-L are well recognized.[6,11]

The disadvantages of e-L are also well described by the participants of this study. Approximately half the participants (45%) believe that not having immediate access to the trainer is a major disadvantage. An online forum, live chat or even the availability of scheduled online meetings could resolve this issue, as well as the other major disadvantage of e-L identified by trainees, namely, their isolation from other learners. Technical issues are also considered a major stumbling block to successful e-L and these could be avoided by providing cross-platform solutions using common standards and protocols such as HTML5 and TCP, respectively.

All participants consider that specialists in vascular surgery would benefit from continuous professional development based on e-L. They also believe that trainees will further develop and improve through the use of e-L programs. All participants consider that classic training and e-L should be combined, depending on the study material and that the Greek vascular society should invest in e-L training. From these results, it is obvious that Greek trainees strongly believe that there is a future place of e-L in both their training and their post-training development. This is also further supported by the answer to the specific question in this regard (see supplementary material). Depending on the training focal point, either classic or e-L training could be used, which echoes the findings of several meta-analyses demonstrating that e-L is not inferior to traditional medical training.[12,13]

The majority of participants (70%) believe that surgical societies should be responsible for developing e-L and one out of five participants (20%) considers that medical schools should develop e-L. This is an dilemma still vexing the majority of the researchers on e-L in medicine and a recent meta-analysis of available resources has not provided a valid answer.[12]

The cost of e-L programs should not burden the trainees (80%), as it should be alleviated by either the surgical societies (15%), sponsors (35%) or partly by the specialist vascular surgeons (30%). In order for an e-L program to be cost effective, a prior market needs assessment should be performed and the e-L program must have a clear focus, a specific target group and clear criteria for assessing the results. In the past, the ESVS e-L team had successfully run a number of different e-L programs that all received >70% satisfaction rate by the trainees who used them.[6,10] Most of these projects were cost-effective as a result of assessing the needs of the target group prior to launching them, a method that contributed to wide participation. The human and material resources required for creating an e-L curriculum are substantial, but these costs are recouped by the ability to host subsequent instalments of the e-L program with fractional further investment.

The final question of the survey was whether a practical (surgical) skill can be taught online. The e-L team of the ESVS explored the application of e-L to the skill of sizing and planning of aortic aneurysm repair with a fully online course based on an open source reconstruction software program that received a high satisfaction score (>70%) from participants.[6,10] In this course, the practical skill was successfully assessed and officially certified by the ESVS, with the caveat that the skill level could not be quantified. This ESVS experience provides a basis for stating that a practical skill can be taught online; this sentiment is further supported by other publications.[14] Limitations exist depending on the practical skill in question, as some skills seem to be easier than others to be taught online.

Other vascular e-L programs, similar to the one previously ran by the ESVS, have been now undergone a radical change on the way they are developed and delivered.[15] Examples of successful vascular e-L programs are been developed by parties not related to official vascular societies, such as groups of health professionals[16,17] or institutions[18].

Since resources are limited and the potential audience is rather limited, a vascular e-L program could be developed and deployed only after a needs analysis is performed and clear educational goals are set. The needs analysis would ideally identify the cohort of vascular professionals that would mainly benefit from an e-L program and what material is necessary to meet the needs of these professionals. Further development would be based on this initial project and the by-then already existing educational platform, reducing further costs and making the Greek vascular e-L program cost-effective and efficient in reaching its aims.

CONCLUSION

e-L for Greek vascular surgeons is still in its nascence, demonstrating both the great promise and the unsolved problems inherent in the early phase of a technology's growth. Although its technical feasibility is continuously gathering supporting data and its results are already described as non-inferior to traditional training, there is still a long way to go before we integrate surgical e-L into our current curricula. Greek trainees demonstrate basic knowledge and understanding of key e-L concepts and believe in the future role of e-L in their training.

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Potential conflicts of interest:
- *VZ is the Representative Greece to EVST*
- *NP is the Honorary Representative Greece to EVST*
- *SM and NP were members of the ESVS e-Learning team*

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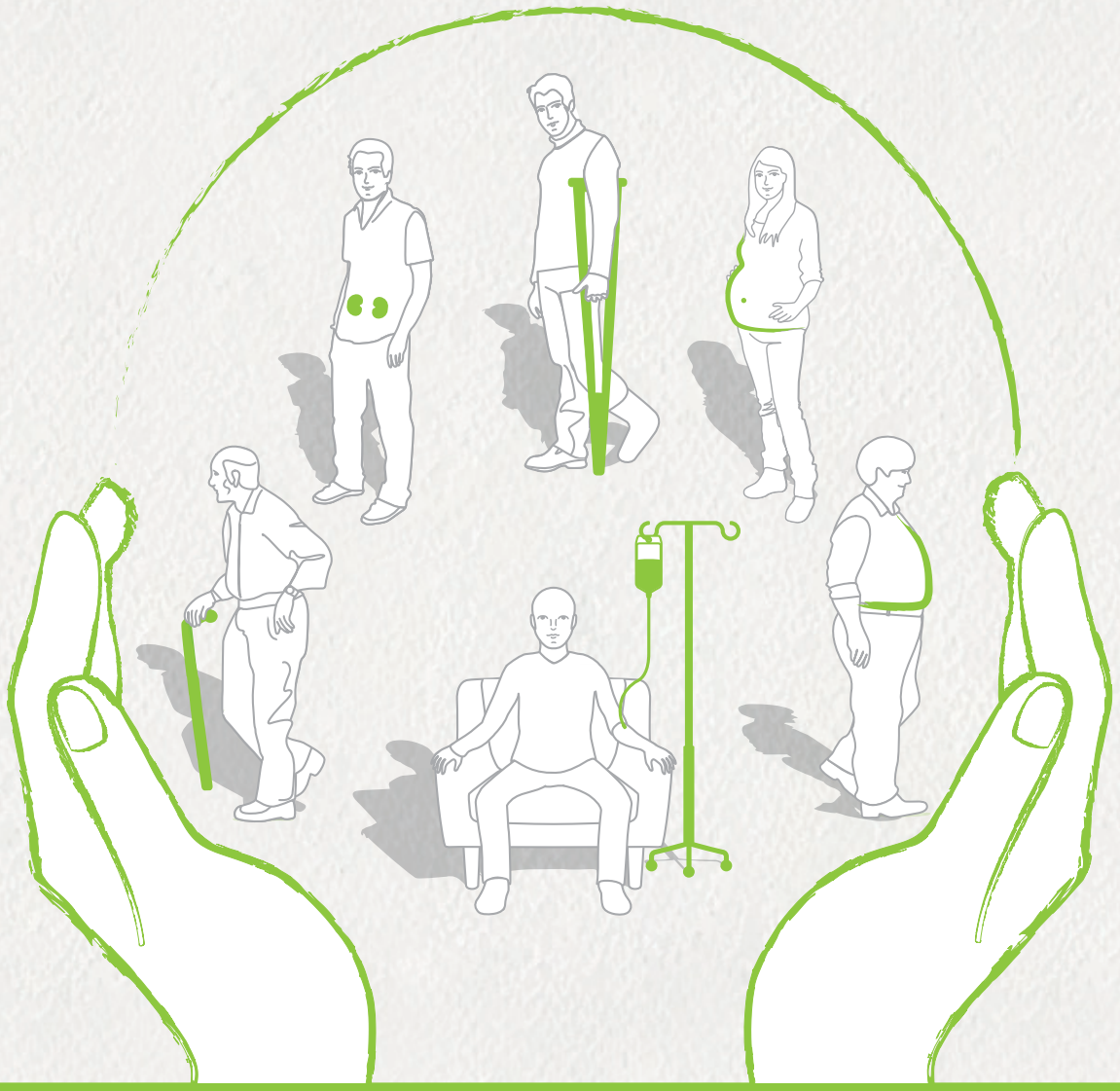

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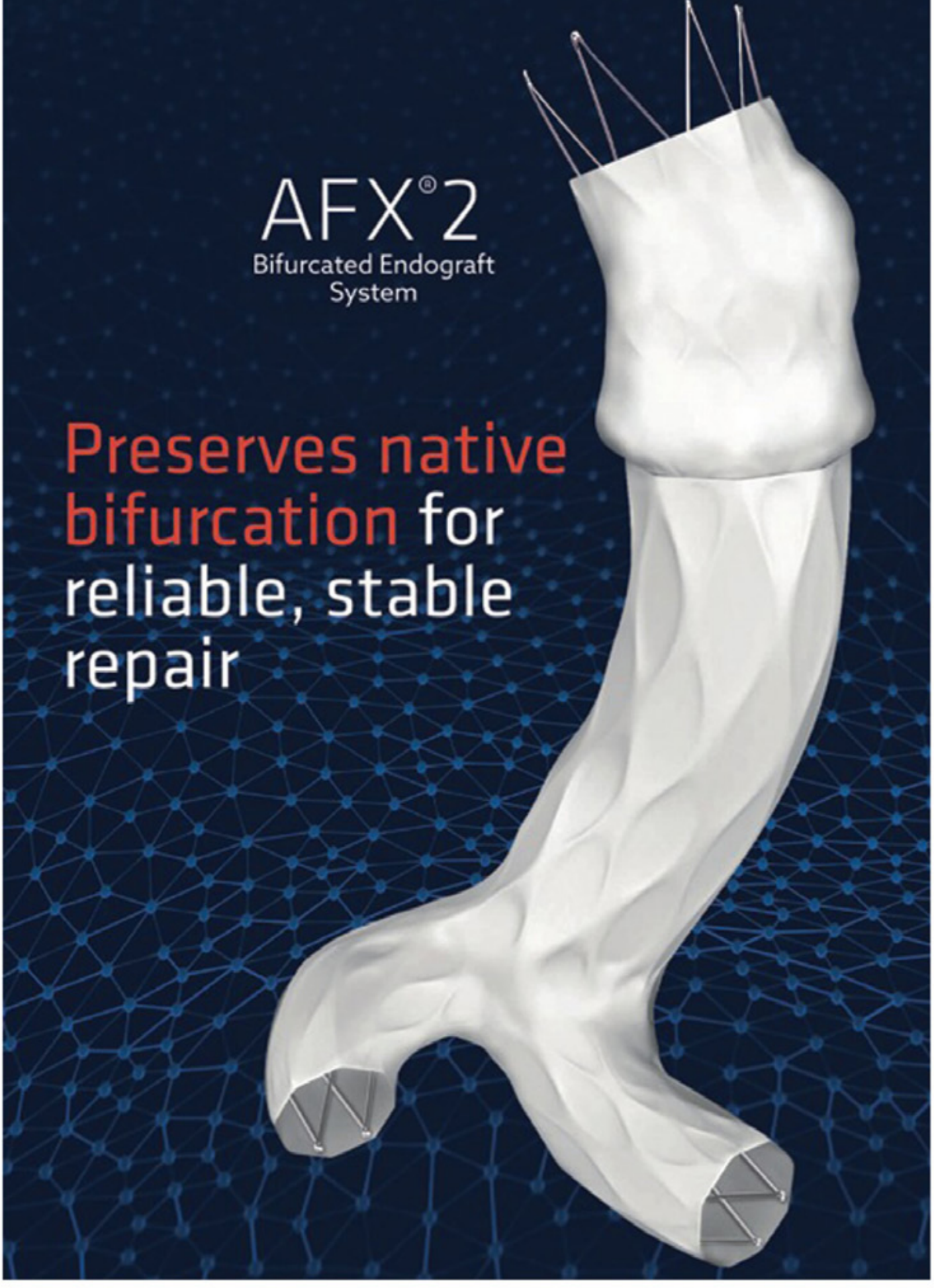

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A symptomatic popliteal venous aneurysm: A case report

Eleni Tsamantioti[1], Chrysanthi P. Papageorgopoulou[2], Stavros Kakkos[2]

[1]Medical School, University of Patras, Patras, Greece
[2]Department of Vascular Surgery, University Hospital of Patras, Patras, Greece

Abstract:

Primary popliteal venous aneurysm (PVA) is a rare condition, with less than 200 cases being reported in the literature. While many patients remain asymptomatic, the majority of them are diagnosed during workup for the venous thromboembolic complications they cause. Due to the high risk of primary or recurrent deep vein thrombosis and pulmonary embolism associated with PVAs, surgical management is usually recommended. We present a case of symptomatic PVA, identified on ultrasound, in a 39-year-old male patient who presented with right leg varicose veins. Natural history studies on PVAs are scarce and expedited repair may be warranted in patients with high risk features for thrombosis like our patient.

INTRODUCTION

Popliteal venous aneurysm (PVA) is a rare vascular disorder, with approximately 200 reported cases in the literature[1]. Venous aneurysm is defined as a persisted isolated dilatation of twice the normal vein diameter[3]. The average diameter of a normal popliteal vein is between 6mm to 8 mm.[4] Popliteal venous aneurysms are the second most common type of venous aneurysms following the internal jugular vein. While many patients remain asymptomatic, the majority of them are diagnosed on workup for the venous thromboembolic complications they cause. Diagnosis can be confirmed by colour duplex ultrasound scanning and computed tomographic venography (CTV) or rarely digital venography[2]. Colour duplex ultrasound scanning has the advantage that it can depict not only the morphology but also blood flow disturbances, such as turbulent and retrograde flow in the aneurysmal segments. The flow information provided by this method, allows a risk assessment of possible thrombus formation in popliteal vein aneurysms. The pathogenesis of PVA remains unclear. PVAs are associated with high risk of deep venous thrombosis (DVT) and pulmonary embolism (PE). The risk for a PE is unforeseeable if the aneurysm diameter is larger than 20mm even with anticoagulant therapy, so surgical treatment is recommended[1]**.** We present a rare case of a PVA in a patient with history of superficial vein thrombosis and signs of venous stasis who developed PVA thrombosis while awaiting repair.

Author for correspondence:

Stavros Kakkos

Department of Vascular Surgery,
University Hospital of Patras, Rio, 26504, Greece
E-mail: kakkos@upatras.gr
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CASE PRESENTATION

A 39-year-old obese man with a past medical history of right leg tremor, presented to the outpatient clinic of our department with symptomatic varicose veins due to great saphenous vein insufficiency of the right lower extremity. He reported two episodes of superficial vein thrombosis of his right leg varicosities some six months ago, treated with a low molecular weight heparin. On preoperative mapping of the right great saphenous vein with Duplex scanning, while checking the small saphenous vein a PVA was incidentally diagnosed, which measured approximately 2.24 x 1.95 cm with signs of venous stasis (donaut sign, Fig.1).

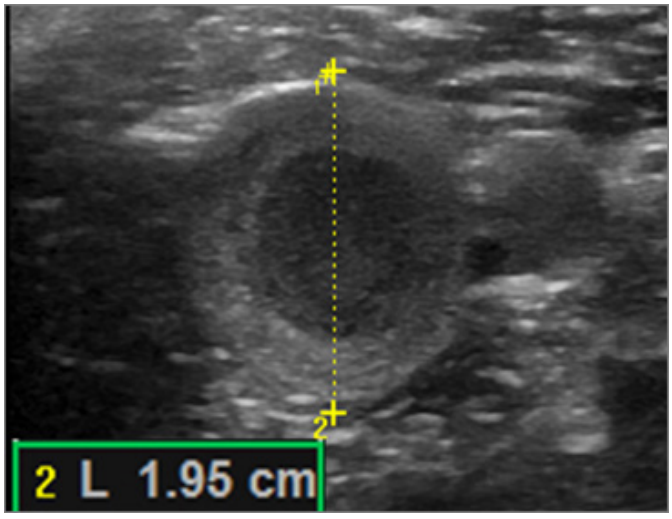

Figure 1. Duplex ultrasound scanning: donaut sign

Following an uncomplicated elective saphenectomy and varicose vein avulsion procedure he was investigated further with magnetic resonance venography, which confirmed the diagnosis of a focal PVA. Three months after the saphenectomy procedure, while awaiting repair of the PVA, our patient

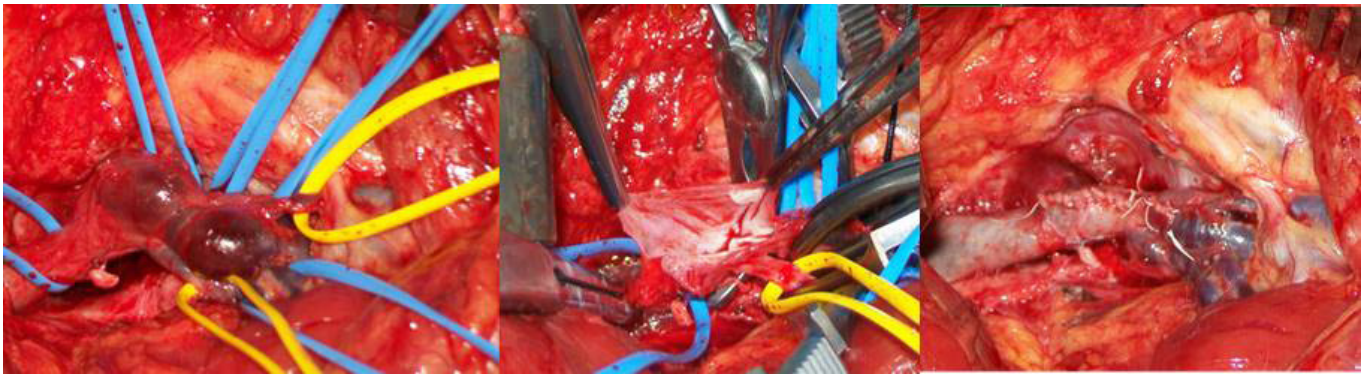

Figure 2. Tangential aneurysmectomy and lateral venorrhaphy of the popliteal venous aneurysm of our patient

developed pain in the right popliteal fossa and was diagnosed as having partial thrombosis of the PVA on Duplex. He was treated initially with tinzaparin 16,000 iu OD subcutaneously switched to apixaban 5mg BID for a total of three months. In order to prevent a recurrent thromboembolic event, after complete resolution of the PVA thrombus on Duplex, we repaired the PVA with tangential aneurysmectomy and lateral venorrhaphy (Fig.2).

Postoperative course was uneventful, and he was discharged on the second postoperative day on enoxaparin 80mg BID switched to apixaban 5mg BID for a month. At six months postoperatively our patient remains asymptomatic, the reconstruction remains patent on color Duplex with no early or late recurrence of thromboembolic events being reported so far. (Fig. 3)

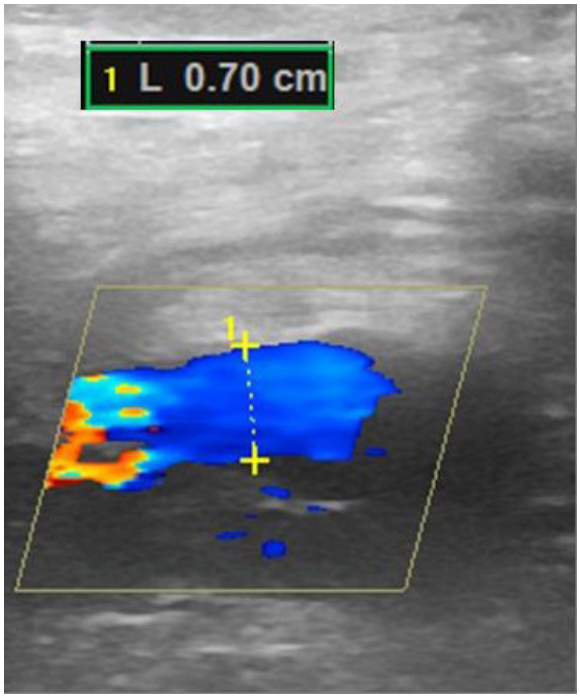

Figure 3. Patency of reconstruction in color Duplex scan during 6-month follow up

DISCUSSION

Aneurysmal dilatation of the popliteal vein is very rare vascular disorder[1]. PVAs are usually left sided and can occur in both sexes with predominance in females**.** Additionally, PVAs have been presented in a wide range of ages. The youngest case reported is a 12 year-old girl with Klippel-Trenaunay syndrome and with a massive PE probably caused by PVA[4]. Due to the fact that PVA can affect both children and adults, a theory has been developed that the dilatation develops progressively in a substrate of damaged, weakened vascular wall.

The etiology of the PVA remains unclear and has been correlated with congenital vascular abnormalities, venous hypertension, traumatic, inflammatory and localized-degenerative conditions[5]. However, the most plausible explanation for their formation is that they are multifactorial; a combination of congenital malformation and mechanical injury. Furthermore, giant PVAs have been observed in Parkes-Weber syndrome, a congenital vascular abnormality defined by limb overgrowth, macro arteriovenous fistula, and capillary-venous deformity[6]. PVAs can be asymptomatic and identified incidentally during the diagnostic approach of venous insufficiency or can present with localized symptoms like swelling or pain[5]. Most of the times , they become clinically obvious causing PE or DVT, conditions with a high rate of morbidity and mortality. In addition, patients with recurrent PE should always be screened for PVA, since the source of emboli is often the aneurysm[1].

Several imaging techniques can be used for the diagnosis of PVA. The initial imaging examination is colour duplex ultrasound scanning , which is sensitive, non invasive and gives the ability to dynamically assess blood flow. In the past, the gold standard imaging technique was venography, which although being more accurate has nowadays been replaced by colour duplex ultrasound scan[8].The types of venography that are being used for the diagnosis of a PVA are computed tomography venography, magnetic resonance venography and invasive digital venography[2].

There is no consensus on which popliteal aneurysms to treat. In asymptomatic cases, with aneurysm diameter less than 20mm, the preferred treatment options are mostly sur-

veillance, anticoagulation or surgery.[9]

It has been shown that the incidence of DVT is directly related to the size of the aneurysm**.** Hence, patients with aneurysm larger than 20mm with or without thrombus should either be treated surgically or receive lifelong anticoagulation therapy[9]. Furthermore, patients with asymptomatic saccular aneurysm, regardless of its diameter, should be treated surgically**.** The treatment options include:

1. Tangential aneurysmectomy and lateral venorrhaphy, followed by low complications if the anatomy permits.
2. Resection of the aneurysm and direct end-to-end anastomosis of the popliteal vein or replacement with a vein graft.[10]

Both of them are performed from the posterior approach, with the patient being placed in prone position. The postoperative treatment consists of anticoagulation therapy for a short period of time and compression stockings of 20 to 30mmHg up to the thigh for three months. The use of vein grafts can be complicated with thrombosis of the vein graft or haematoma, requiring further treatment. Hence, tangential aneurysmectomy and lateral venorrhaphy is the preferable surgical treatment, due to fewer complications.[10]

CONCLUSION

We present a rare case of a PVA in a patient with history of superficial vein thrombosis and signs of venous stasis who developed PVA thrombosis while awaiting repair. Natural history studies on PVAs are scarce and expedited repair may be warranted in patients with high risk features for thrombosis like our patient.

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Can a routine, bedside procedure result in a catastrophe? A clinical paradigm of severe complications following attempts to catheterize the subclavian vein

Stavros Charalambous[1], Nikolaos Kontopodis[2], Alexandros Kafetzakis[2], Nelli Kholcheva[1], Christos Ioannou[2], DimitriosTsetis[1]

[1]Interventional Radiology Unit, Department of Medical Imaging, University of Crete, Medical School, Greece
[2]Vascular Surgery Unit, Department of Cardiothoracic & Vascular Surgery, University of Crete, Medical School, Greece

Abstract:

Introduction: Central venous catheterization is a routine clinical procedure but possible complications, although rare, can be potentially serious.

Case description: We report a rare case of two concurrent left subclavian artery pseudoaneurysms, secondary to a complicated left subclavian vein catheterization. The first became apparent at the time of catheter removal and was treated by percutaneous thrombin injection while the second became obvious only 7-days later, after causing compressive symptoms and was successfully repaired with endovascular-stenting. This case was further complicated by myocardial ischemia resulting from manipulation of a patent internal mammary artery which was serving as a graft during a previous coronary bypass.

Conclusions: Catheter malposition during central vein cannulation may occasionally cause serious adverse events. Cardiac complications should be anticipated in case a patent internal mammary artery supplies oxygenated blood to the coronary circulation. A wide range of endovascular modalities can be used to successfully treat these lesions.

INTRODUCTION

Central venous cannulation is an essential, routine bedside procedure performed in hospitalized patients for various reasons.[1] Accidental arterial puncture occurs in 5% and subclavian artery pseudoaneurysm is a rare clinical entity with only few cases reported.[2-6] Traditional open repair of these lesions remains a safe treatment option but the site of arterial injury is difficult to expose, while comorbidities make surgical correction challenging for critically ill patients. Endovascular repair with covered stents, percutaneous closure devices and pseudoaneurysm embolization has been reported to offer good results when selected appropriately.[4-7]

We present a case of two concurrent left subclavian artery pseudoaneurysms, after an attempted left subclavian vein (SCV) catheterization. These were successfully repaired with thrombin injection and endovascular stenting in two time points.

CASE DESCRIPTION

A 75-year-old patient with a background history of myasthenia gravis, coronal artery bypass grafting (CABG), synthetic aortic valve replacement, diabetes mellitus and peripheral arterial disease presented in Vascular Surgery Department with foot gangrene. During his hospitalization, SCV catheterization without ultrasound guidance was attempted on the left neck side for hemodynamic monitoring and fluid administration. After multiple attempts, a temporary 7-French triple-lumen catheter was inadvertently positioned in the left subclavian artery. Subsequently, the patient was transferred to the Interventional Radiology Unit for catheter removal under fluoroscopic control.

Through the left brachial artery a 0.035" stiff hydrophilic guidewire was advanced into the origin of the left subclavian artery. A 5-French diagnostic catheter was introduced and diagnostic digital subtraction angiography (DSA) was performed. DSA revealed a small-sized pseudoaneurysm originating from the left subclavian artery measured approximately 1.2x0.7cm with a neck length of 3mm and width of 2mm, in close proximity with left vertebral (LVA) and internal mammary arteries (LIMA). The tip of the triple-lumen catheter was in direct contact with the false sac.(Figure 1) Left common carotid artery, LVA and LIMA remained intact. Due to the close proximity of the arterial injury to the origin of LVA and LIMA, deployment of a stent-graft would carry the risk of their coverage which would be particularly insecure, especially taking into account the patent IMA that was serving as a coronary artery bypass graft. Alternatively, 2000 IU of thrombin were injected into the lumen of the false aneurysm, though the triple-lumen catheter. The narrow neck of the pseudoaneurysm and the fact that the tip of the catheter was inside the false sac, made the lesion amenable to such a manipulation. The pseudoaneurysm immediately thrombosed without any compromise of the arterial branches. (Figure 2)

Author for correspondence:

Nikolaos Kontopodis, MD, MSc, PhD

Vascular Surgery Unit, Department of Cardiothoracic and Vascular Surgery, University Hospital of Heraklion, University of Crete Medical School, PO-Box 1352, 711 10, Heraklion, Greece
Tel: +30 2810392379, +30 6948202539
E-mail: kontopodisn@yahoo.gr
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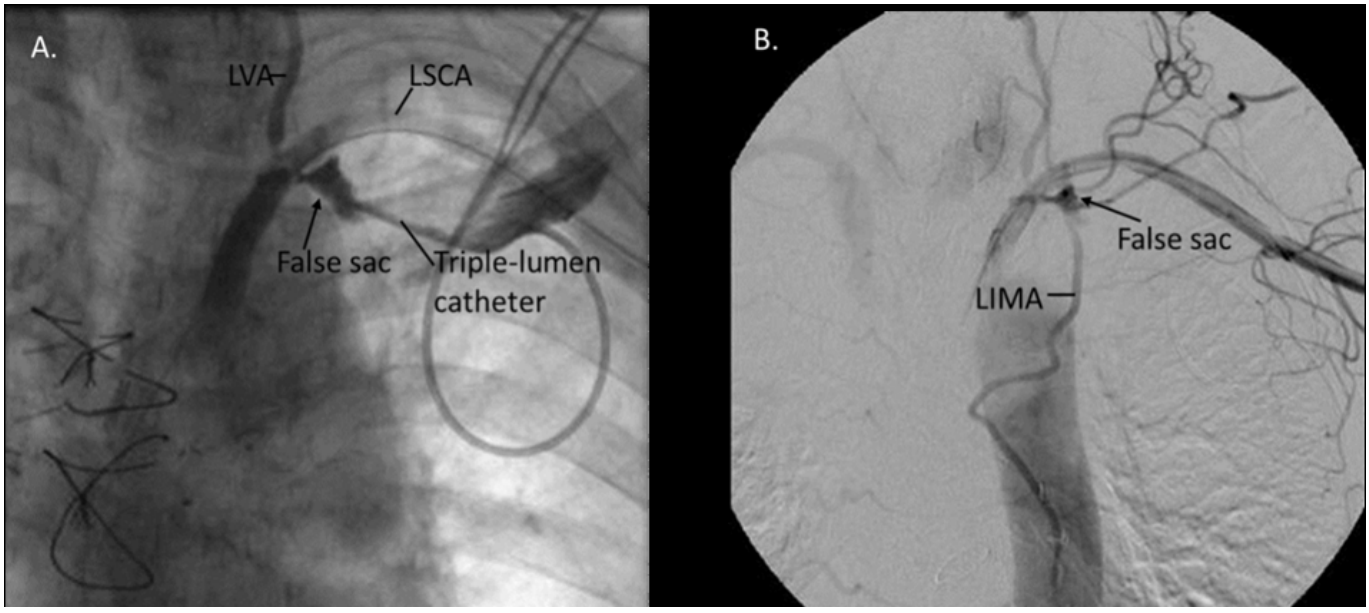

Figure 1: Angiography through triple-lumen catheter (fig A) and diagnostic catheter (fig B). Pseudoaneurysm mass (false sac) measured approximately 12x7 mm with a neck of 3mm length and 2 mm of width, that originated from left subclavian artery, found to be in a direct contact with the triple-lumen catheter. Left vertebral and internal mammary arteries remain intact.

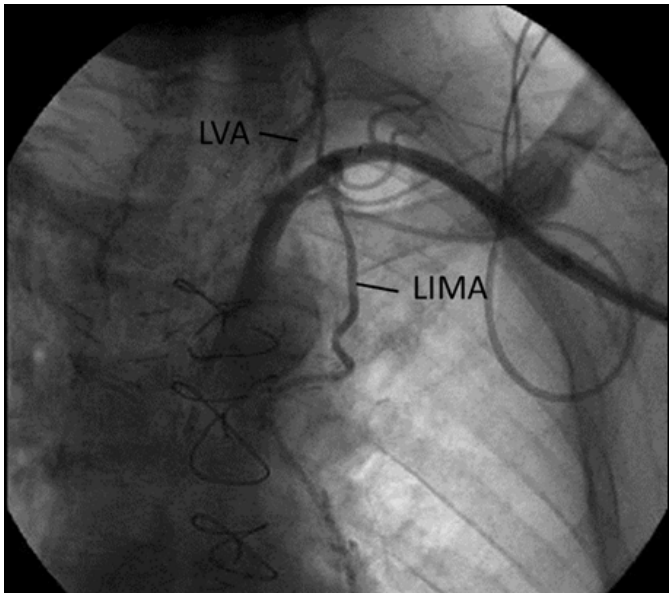

Figure 2. Post-thrombin injection. Diagnostic subtraction angiography shows immediately thrombosed aneurysmal sac, without any compromise of the left vertebral and internal mammary arteries.

The 1st post-procedural day the patient complained about thoracic pain and presented electrocardiographic changes with ST-elevation while troponin level had increased. Myocardial ischemia was diagnosed and he was transferred to the cardiology intensive care unit for further management. This was believed to be a complication resulting from leakage of thrombin into the LIMA.

Seven-days after the percutaneous thrombin injection with the patient having recovered from his cardiac condition, he reported difficulties in breathing and swallowing which were associated with neck swelling. Emergent CT angiography revealed a second pseudoaneurysm measured approximately 5x3x4 cm in the upper side of the chest and neck region, originating from the left subclavian artery, few millimeters away from the origin of the LVA and LIMA and at the opposite side of the previously thrombosed, early pseudoaneurysm which caused a mass effect and mediastinal shift. (Figure 3).The possible mechanism was hypothesized to be the initial arterial puncture which went completely through the subclavian artery.

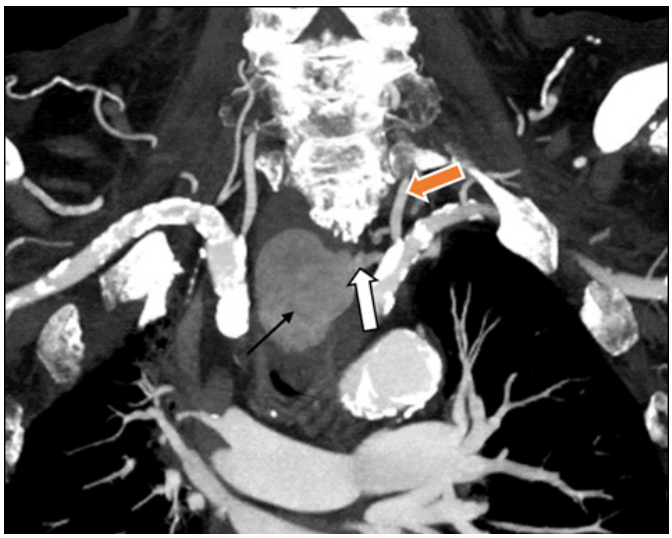

Figure 3. Computer tomography-aortography. Coronal view/MIP reconstruction. A large paravertebral mass (black arrow) at the level of T8 vertebra, causing compression over the trachea and esophagus. The mass found to be in contact with left subclavian artery, few millimiters away from left vertebral (orange arrow) and left internal mammary arteries. Leakage/exavasation of intravenous contrast is demonstrated from the posterior wall of subclavian artery, through a discrete neck of 2cm lengh and 3-4mm width (white arrow) into the paravertebral mass (pseudoaneurysm).

The patient immediately was transferred to the interventional radiology unit for further management. Endovascular subclavian artery stenting was offered and the procedure was performed through the left brachial and left femoral arteries using 5-French and 10-French sheaths, respectively. Through the brachial access, a 0.014" hydrophilic guidewire and 3x15mm balloon catheter was advanced into the LIMA, in order to maintain access if accidentally this had blocked. Through the femoral access, a 0.035'' stiff hydrophilic guidewire and a 5-French diagnostic catheter were advanced into the left subclavian artery and DSA was performed. A 7x40mm balloon expandable covered stent was advanced and positioned to the left subclavian artery immediately proximal to the origin of the LIMA which remained intact. The completion angiography demonstrated the correct position and expansion of the stent-graft. (Figure 4)

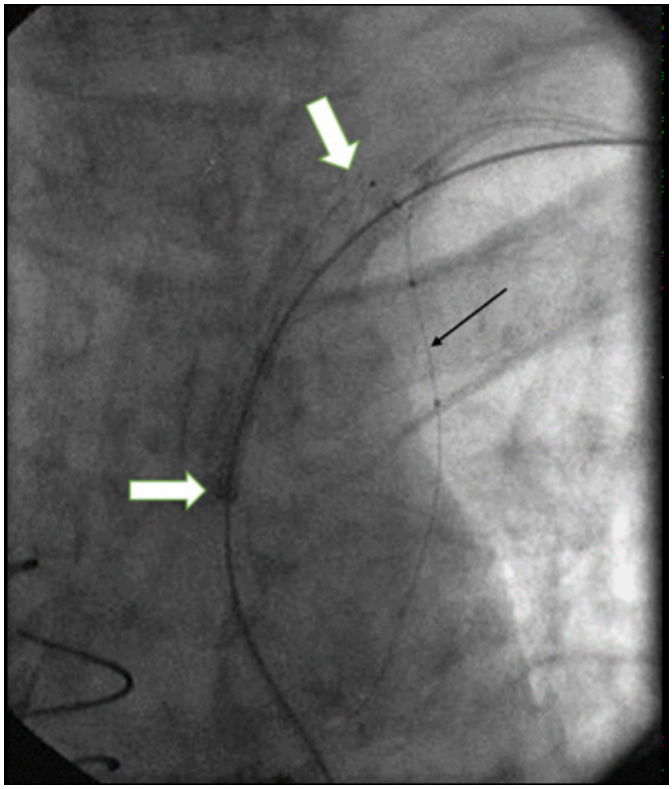

Figure 4: Endovascular repair using covered-stent. The stent-graft 7x40 mm (between white arrows) was positioned in the left subclavian artery, few millimeters from left internal mammary artery. In advance, balloon 3x15mm (black arrow) was advanced over 0.014'' guidewire into the internal mammary artery.

DISCUSSION

Central venous cannulation is a routine clinical procedure, which nevertheless carries specific risks. Various complications have been described which are rare but potentially serious.[8] Although venous puncture using surface anatomic landmarks has been widely practiced, ultrasound guided cannulation has been reported to result in higher success rates and fewer complications.[4]

If arterial cannulation occurs with large catheters (>7 French), it is suggested to keep the CVC in place, and perform a safe removal under direct visualization.[2] Pseudoaneurysms are rare and usually occur immediately after an iatrogenic injury but delayed manifestations are possible.[4-6] Since spontaneous rupture and thrombosis are common risks, immediate correction is recommended.[4] Several options are available, ranging from the traditional open repair to minimal invasive techniques, like balloon occlusion, endovascular stents, percutaneous closure devices, thrombin injection and coil embolization.[4-7] Stent-grafts present a high technical success rate but carry the risk of arterial branch occlusion.[7] Balloon tamponade offers technically feasible and effective hemostasis but prolonged balloon dilatation may lead to limb ischemia, thromboembolism, delayed pseudoaneurysm formation and additional risks for myocardial damage in cases of CABG.[7] Therefore, management of these lesions should be individualized and selected based on imaging evaluation. In our case, close proximity of the pseudoaneurysm with the origin of the LVA and a patent LIMA coronary bypass made hemostatic ballooning or stent-graft insertion insecure and therefore thrombin injection was favored as the safest treatment option.

The delayed presentation of the second pseudoaneurysm underlines the need for continuous monitoring and a high suspicion index. Although not typical, delayed presentation has been previously described.[9] This can be attributed to the continuous slow leakage of a small quantity of blood from the injured vessel. The fact that the patient was anticoagulated due to his prosthetic aortic valve, may have played a role. Another remarkable point is the myocardial ischemia which complicated recovery of our patient after thrombin injection. Such a complication most likely occurred due to the close proximity of the arterial injury to the LIMA origin. This highlights the fact that direct injury of a patent IMA coronary graft is possible during attempts to puncture the SCV. Accordingly it would be reasonable to recommend that the side of the origin of an IMA coronary bypass graft should be preferentially avoided.

Finally, the fact that two concurrent pseudoaneurysms complicated the procedure has not been previously reported and may be explained by a throughout arterial puncture, during attempts for vein cannulation. Thus, if vein cannulation is challenging and unsuccessful after several attempts, a safe strategy would be to abandon the procedure, seek assistance, use real-time ultrasound or try alternative access sites. Aggressive, continuous attempts for cannulation are ill-advised and may result in catastrophic outcomes.

CONCLUSION

Iatrogenic subclavian artery pseudoaneurysms can be safely managed by endovascular means, using a wide range of therapeutic options and a patient- and lesion-specific approach. A high suspicion index is necessary in order not to miss delayed manifestations, while cardiac complications should be anticipated in case a patent IMA bypass graft.

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No conflict of interest

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Severe complications after intravascular application of bone cement and hemostatic agent during posterior spinal surgery

Bernadette Bachofen, Roman Bühlmann, Thomas R. Wyss, Vladimir Makaloski

Department of Cardiovascular Surgery, University Hospital Bern, Bern, Switzerland

Abstract:

Purpose: Posterior surgical approaches to the lumbar spine may cause vascular injuries because of their proximity to the large abdominal and pelvic vessels.

Case report: We describe three patients with intraarterial and intravenous application of bone cement and/or hemostatic agents during posterior surgical approach to the lumbar spine. One patient required urgent thrombectomy after acute iliac artery occlusion with severe leg ischemia. One patient received infrarenal aortic repair and bilateral infragenual bypasses after severe bilateral ischemia due to acute thrombosis of the infrarenal aorta. This patient died on day 3. One bone cement embolization of the inferior vena cava was treated conservatively.

Conclusion: The use of bone cement and hemostatic agents when arterial bleeding occurs can lead to unnoticed application in large vessels with devastating outcome. Early diagnosis and prompt re-vascularization is crucial. Intravascular solid cement plug and foamy reaction of the hemostatic agents allows very limited endovascular treatment options.

HIGHLIGHTS

Intravascular application of hemostatic agents or cement can have fatal outcome.

During lumbar surgery in prone position ischemia or relevant bleeding can be missed.

Being aware of this complication can change the approach when bleeding occurs.

INTRODUCTION

There is a low risk (0.1%) for vascular complications in spinal surgery.[1] However, in the lumbar spine area large vessels are in proximity, thus increasing the risk for vascular injury. The risk seems to be higher during posterior approach in the lumbar area.[2, 3] Different mechanisms can lead to injury of the large vessels: transpedicular drill holes, use of graspers during disc surgery and/or mal-positioned screws.[2, 3, 4] In spinal surgery the fractured or osteoporotic vertebral bodies are filled with bone cement and hemostatic agents are often used, when smaller venous bleeding occurs after drilling. We report three cases with accidental intravascular application of bone cement and hemostatic agents during posterior spinal surgery in prone position.

Author for correspondence:

Bernadette Bachofen

Department of Cardiovascular Surgery, University Hospital Bern, University of Bern, Freiburgstrasse 18, 3010 Bern, Switzerland

E-mail: bachofen@usb.ch

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REPORT I

A 56-year-old year old female required re-do decompression due to re-stenosis of the neural foramen L3-L4 with left-sided radicular leg pain. After decompression via posterior approach in prone position, massive bleeding started from a right-sided pedicle screw hole after removal of an old screw. Hemostatic agents (Surgiflo®, Ethicon and Traumastem®, Bioster) were used to control the bleeding. After completion of procedure the patient had right-sided acute lower limb ischemia. Computed tomography angiography (CTA) revealed an occlusion of the right common iliac artery (CIA) with intra-arterial air. (Figure 1A). The empty screw hole reached the right CIA. Immediate balloon-embolectomy of the iliac and femoral vessels from the groin restored circulation to the leg. Foamy looking tick thrombus was removed. Intraoperative angiography showed no bleeding from the iliac vessel and extensive embolization of multiple small arteries in the leg. (Figure 1B)

The postoperative course was uneventful and the patient was discharged with single antiplatelet therapy. After one year all vessels in the right leg were patent and the pedal pulses palpable, but the patient reported severe claudication in leg. This claudication might have vascular origin due to embolization of very small arteries without sufficient collaterals or a neurologic origin arising from the lumbar degeneration.

REPORT II

A 72-year-old-female patient with chronic occlusion of both superficial femoral arteries required extended re-decompression at the level of L3-S1 with spondylodesis Th11-S2 and sacral vertebroplasty in prone position due to debilitating lumbar pain caused by pseudoarthrosis and sacral fracture. Massive bleeding occurred after removal of an old screw and stopped after application of hemostatic agents (Surgiflo®

Ethicon; Tachosil® Takeda). Additional bone cement was applied in the drill hole for reinforcement of the new screw. After extubation the patient complained of continuous unmanageable pain in both legs. The CTA showed complete thrombosis of the infrarenal aorta and iliac arteries with intra-arterial presence of airy thrombus and bone cement. (Figure 2A). The left common iliac artery was perforated with the tip of a new screw. Simultaneous revascularization with bifurcated aorto-bifemoral graft, removal of cement and thrombus from the groin and infragenual femoro-popliteal bypasses followed. After completion of the proximal anastomosis, shunts were connected to the legs of the bifurcated graft and inserted in the right deep femoral artery and left below-knee popliteal artery. Massive foamy airy thrombus and cement was extracted from all occluded vessels. Massive muscle necrosis in both legs induced acute kidney injury resulting with extremely increased potassium level and malignant arrhythmias. Immediately initiated hemofiltration couldn't correct sufficiently the potassium blood level. The patient died due to multi organ failure on day three postoperatively.

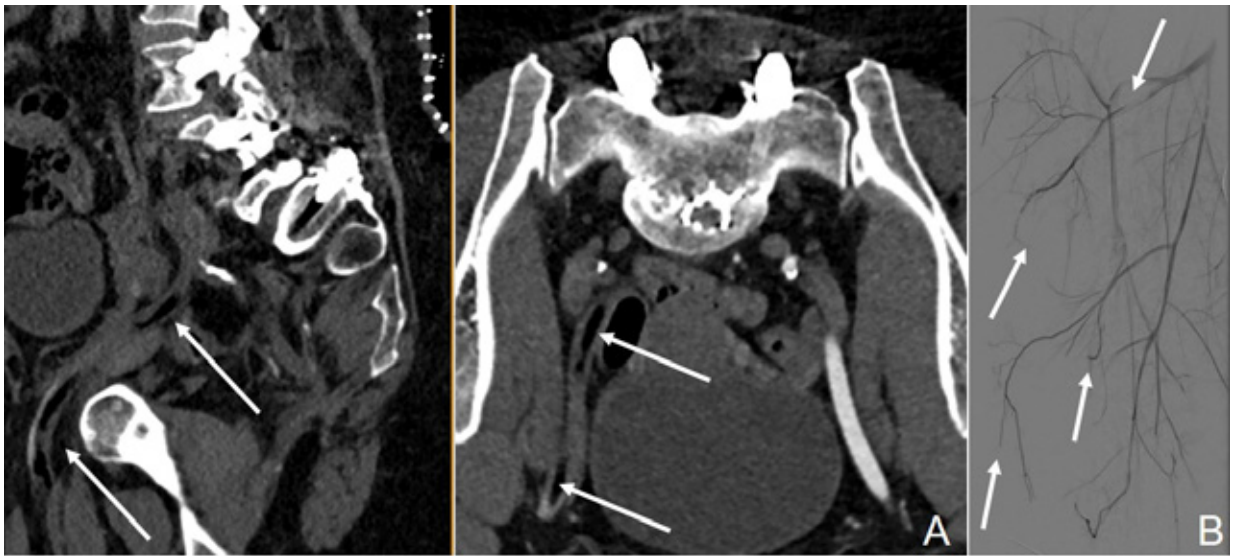

Figure 1. A: Figure 1. A: preoperative computer tomography angiography with foamy airy thrombus (white arrows) in the thrombosed right external iliac artery; B: intraoperative angiography of the right deep femoral artery with residual foamy thrombus and occluded small peripheral arteries (white arrows)

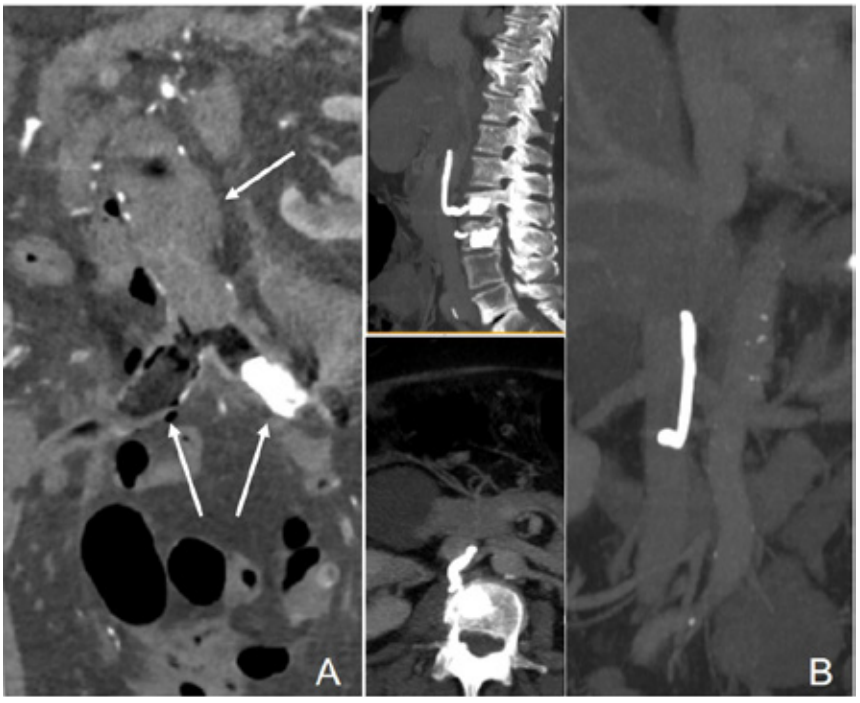

Figure 2. A: Thrombosed infrarenal aorta with bone cement in the left and foamy thrombus (white arrows) in the right common iliac artery; B: bone cement plug in the inferior vena cava

REPORT III

A 77-year-old female patient experienced spontaneous fracture and required bone cement vertebroplasty of L2-L3. After uneventful operation the postoperative CTA revealed a long cement plug beginning from the L2 vertabrae and ending in the inferior vena cava. (Figure 2B) This embolization probably occurred via unintentional direct puncture of the posterior wall of the inferior vena cava, thus explaining the plug continuity. There was no additional peripheral pulmonary embolization. The patient was discharged on anticoagulants.

DISCUSSION

Large vessel lesion with bleeding after spinal interventions is a well-described complication.[2,3] Prompt diagnosis in prone position during posterior approach remains difficult. Endovascular treatment with stent-grafts is a good option in case of bleeding from large vessel and with embolization and coiling after bleeding from lumbar veins/arteries.[4,5] Misplaced screws with potential vessel involvement remain clinically silent. Re-do surgery with removal or screw exchange has higher risk for bleeding complications.[1] Routine CTA prior to re-do spine surgery with posterior approach might help revealing misplaced screws and avoid potential vascular complications. In cases with intraarterially placed screws, placement of a stent-graft could be an option to avoid bleeding after screw removal.

On contrary, large vessel occlusion after intravascular application of bone cement or hemostatic agents is a rare condition. Intravascular hemostatic agent causes extensive local reaction with foamy occlusion and peripheral embolization. Endovascular removal of this foamy thrombus or local lysis is questionable. Open surgery with balloon-embolectomy is a fast and good solution to retrieve the foamy thrombus from the vessel. The occlusion of small peripheral arteries with completely patent femoro-popliteal axis was probably the reason for severe leg claudication in the first patient.

There is no endovascular option to remove intravascular bone cement. In the second patient no wire or balloon-catheter passage was possible from the groin. The open access to large abdominal and iliac vessel with complete removal of intravascular cement plug remains the fastest option to restore circulation in lower extremities.

Due to its fixation to the vertebral body the intracaval cement plug ended without severe complication in the third patient. Potential lethal outcome could be expected if similar cement amount would end in the pulmonary vessels.

CONCLUSION

In case of significant bleeding during re-do spine surgery, large vessel injury should be assessed before using cement and hemostatic agents as the intraarterial placement of these agents can be fatal. Hemostatic agents and cement should not be used without identification of the bleeding source. Early diagnosis and prompt re-vascularization is crucial.

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Surgical approach of a giant intra-parenchymal renal artery aneurysm associated with arteriovenous fistula in a woman with solitary kidney: A report of a case

Kyriakos Ktenidis, Vasiliki Manaki, Alexia Gabriilidou, Eleni Kourtellari, Dimitra Pagkou, Michail Gionis, Argyris Giannopoulos

Vascular Surgery Department, AHEPA University Hospital, Aristotle University of Thessaloniki, School for Health Sciences, Faculty of Medicine, Thessaloniki, Greece

Abstract:

Background: Renal artery aneurysms (RAAs) and renal arteriovenous fistulas (RAVFs) are uncommon lesions and they rarely occur concomitantly. While less than 10% of RAAs are intra-parenchymal, they are usually multiple and they may be associated with AVFs. Treatment of these lesions should always be considered on the basis of the location of the RAA and AVF.

Case Report: The case reported is a RAA with a concomitant high-flow AVF of the right kidney. Due to the size and location of the aneurysm and AVF hemodynamics, endovascular therapy was rejected by the interventionalists, and open repair through right nephrotomy and partial aneurysmatectomy was considered as best surgical option.

Conclusions: Renal artery aneurysms with concomitant arteriovenous fistula are extremely rare and their surgical approach is very demanding.

INTRODUCTION

Renal artery aneurysms (RAAs) represent an uncommon clinical entity, with an estimated incidence of 0.01-0.09% in the general population. They account for 0.01-0.5% of all aneurysms[1,2]. Intra-parenchymal renal artery aneurysms are extremely rare. They are detected in less than 10% of all patients with RAAs[3]. Lesion's diagnosis is usually an incidental finding (increasing the incidence of RAAs), as patients are investigated for other pathologies. Management of these vascular lesions remains controversial. Renal arteriovenous fistulas (AVFs) are abnormal communications between the intrarenal arterial and venous systems[4]. AVFs are relatively rare, with an estimated incidence of less than 0.04%. First to report an intrarenal arteriovenous fistula was Varela in 1928. They can be congenital, idiopathic, or acquired. The case presented in this article is characterized by the simultaneous presence of an intra-parenchymal RAA of very large dimensions and an AVF, which is rarely reported in the literature[4-8]. In almost all published cases, the AVF formation has been associated to a RAA rupture into an adjacent intraparenchymal vein. This mechanism is due to the close proximity of the vein, which first becomes compressed and then stretched by the adjacent aneurysm. Finally, erosion of the aneurysmal sac and the vein wall (with concomitant rupture into the vein) occurs.

Author for correspondence:

Kiriakos Ktenidis

Vascular Surgery Department, AHEPA University Hospital of Thessaloniki, Greecee
E-mail: kirktenidis@gmail.com, info@kktenidis.gr
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CASE PRESENTATION

A 44-year-old woman was admitted electively to our institution for surgical management of a large (28.3 mm x 35.6mm) intra-parenchymal renal artery aneurysm (RAA) [Fig. 1] associated with arteriovenous fistula (AVF) of the right kidney. Her past medical history included left total nephrectomy, [Fig. 1] secondary to RAA rupture and total avulsion of the left kidney during the 27th week of pregnancy.

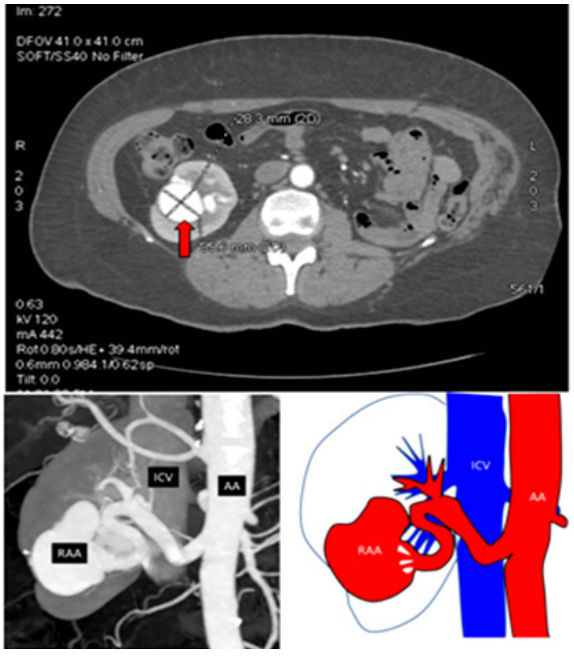

Figure 1. Computed Tomography (A: transversal CTA-aneurysm formation and its dimensions, B: 3D-CTA intra- parenchymal renal artery aneurysm in patient with solitary kidney and schematic representation)

Patient had no hypertension or other comorbidities. Aneurysm was detected during her last follow-up, in a routine abdominal examination due to her anamnesis. Operating procedure was performed with the patient in a left lateral decubitus position and lateral subcostal laparotomy between the iliac crest and the 12th rib. Retroperitoneal approach allowed identification and dissection of the hilus vessels. Secondary to vessel control with vessel loops, identification of the subcapsular aneurysm was feseable. The aneurysm was located between the middle part and the caudal pole of the kidney [Fig. 2].

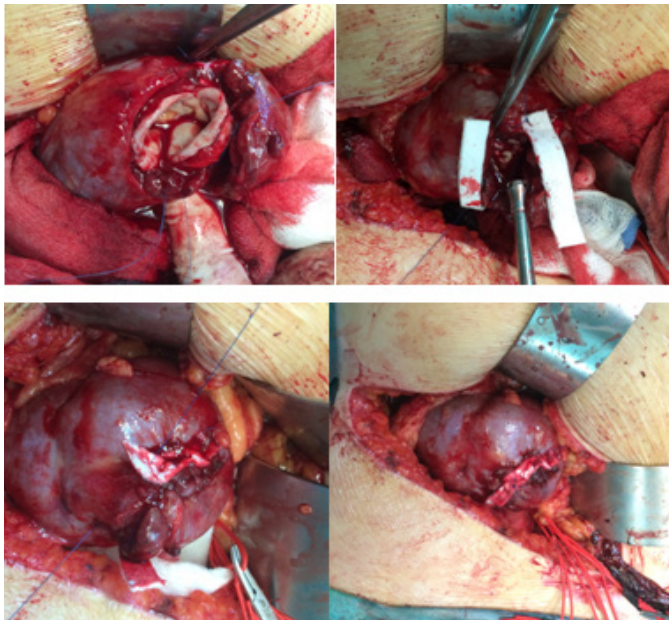

Figure 2. The intra-parenchymal aneurysm of the renal artery, perioperative picture

Five thousands IU of unfractioned heparine (UFH) were administrated bolus, i.v., and peripheral nephrotomy with partial preparation of the aneurysmal sac and temporary vascular occlusion (unselected cross clamping of renal vessels) was performed [Fig. 3]. Incision of the aneurysmal sac (aneurysmatectomy) permitted an-at first sight- identification of the internal shunt, as well as identification and ligation of the origins of the inflow and outflow vessels with a 4-0 Polypropylene suture. Teflon pledgets were used to best seal the sutures. After partial aneurysmal sac resection [Fig. 2, 3] meticulous hemostasis of the parenchymal margins, and nephrotomy, the wound was closed in anatomic layers [Fig. 3]. The total duration of arterial and venous clamping was 23 min. Four units of red blood cells (RBC) were administered perioperatively, whereas the in-hospital post-operative period was uneventful. The patient was discharged on the 8th postoperative day in good clinical condition. Histological examination revealed degenerative aneurysmal disease. Thromboprophylaxis with Bemiparin 2500 IU/dl was administrated perioperatively and 100 mg of aspirin was prescribed for a 6 month period after surgery. In a two-years follow-up with Duplex scan to avoid contrast administration, patient's renal function showed no deterioration.

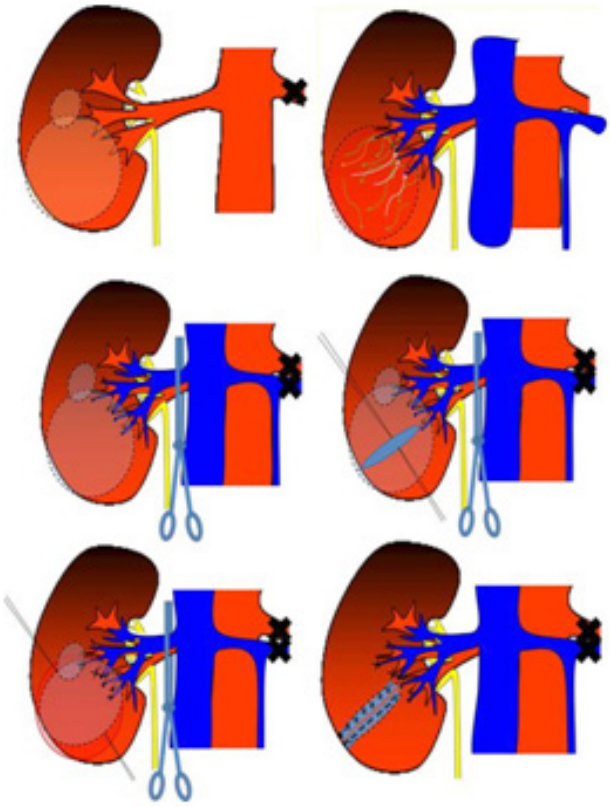

Figure 3: Schematic representation of the surgical procedure (A: localization of arterio-venous aneurysm formation, B: renal vessel cross-clamp and nephrotomy, C: partial aneurysmatectomy, suturing in anatomic layers step by step)

DISCUSSION

Coexistence of a RAA and an AVF is a rare condition[4-8]. RAA is defined as a 200% increase in the diameter of a normal renal artery[1,2]. Symptoms consist of flank pain, hematuria, renal infarction secondary to embolization and uncontrolled hypertension resistant to medical management. Indications for treatment of RAAs are rupture, rapid expansion, pregnancy, or aneurysm diameter > 2 cm[1,2]. Based on the treatment options for RAAs, Rundback et al proposed an angiographic classification system: Type 1 RAAs are saccular lesions arising from either the main renal artery trunk or from a proximal large segmental artery[9]. These aneurysms can be treated with stent grafts or coil embolization (endovascular repair)[10-11]. Open repair of Type 1 lesions includes excision and primary revascularization or patch angioplasty, with an autologous vein, or a PTFE graft[9]. Type 2 RAAs are fusiform and usually located at the main renal trunk, or at the proximal segmental arteries[9]. These are best treated surgically with segmental excision of the aneurysm and arterial reconstruction with an end-to-end small autologous tube graft or with aorto-renal by-pass grafting (in patients with no autologous veins available, a 6mm PTFE graft can be an option). Type 3 lesions are intra-parenchymal aneurysms involving the small, segmental or accessory arteries[9]. Type 3 aneurysms, due to their intra-parenchymal location are best treated with coil embolization (endovascular repair)[9].

In the era of endovascular repair, it is of high importance to evaluate every surgical option and deliver optimal individualized treatment in order to achieve the best medical outcome. This case-report refers to a Type 3 RAA combined with a high-flow AVF treated in our institution. These lesions, due to their intra-parenchymal location, are best treated with coil embolization. Nevertheless, due to the large dimensions of the RAA and the high-risk of embolization due to AVF high hemodynamics, segmental nephrectomy was performed on the basis of a safer outcome.

CONCLUSION

Renal artery aneurysms with concomitant arteriovenous fistula are extremely rare. Open repair approach is a safe and effective option even in cases with challenging anatomy.

No conflict of interest.

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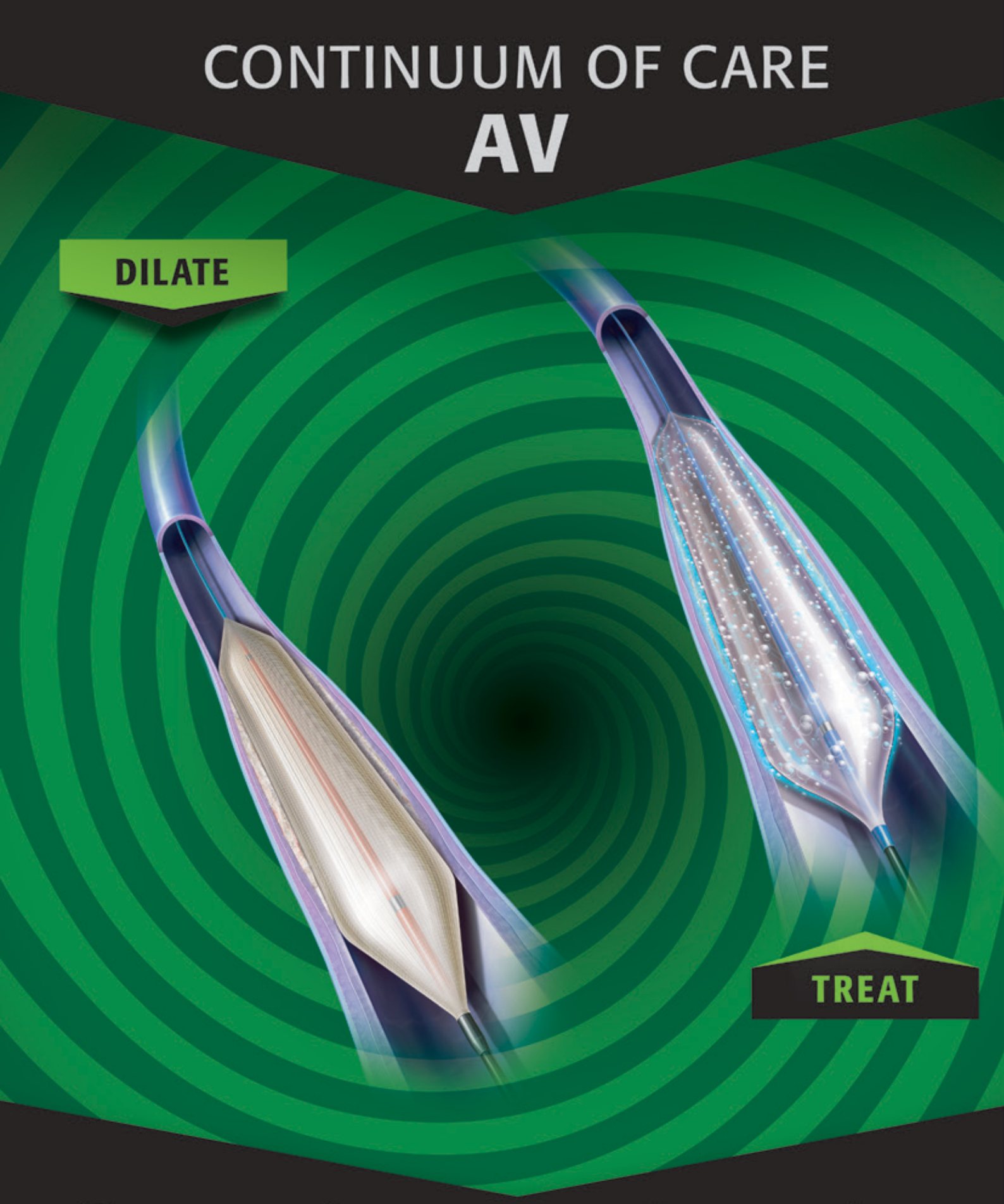

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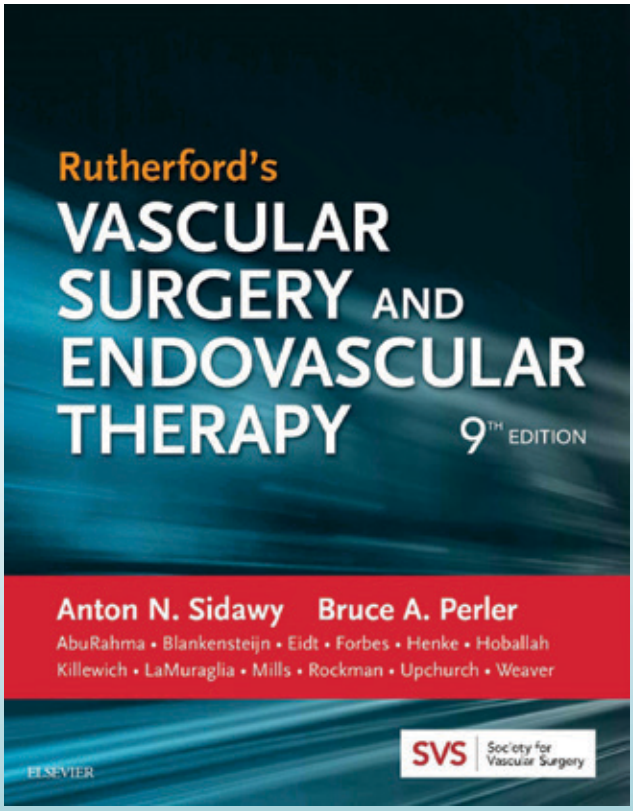

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