Vanessa Elizabeth Carolina Pourier

Clinical approaches in the treatment of extracranial carotid artery aneurysms

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Clinical approaches in the treatment of extracranial carotid artery aneurysms

Klinische benadering bij de behandeling van extracraniële carotis aneurysmata
(met een samenvatting in het Nederlands)

Proefschrift

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door

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geboren op 13 november 1985 te Willemstad, Curaçao

Promotor: Prof. dr. G.J. de Borst

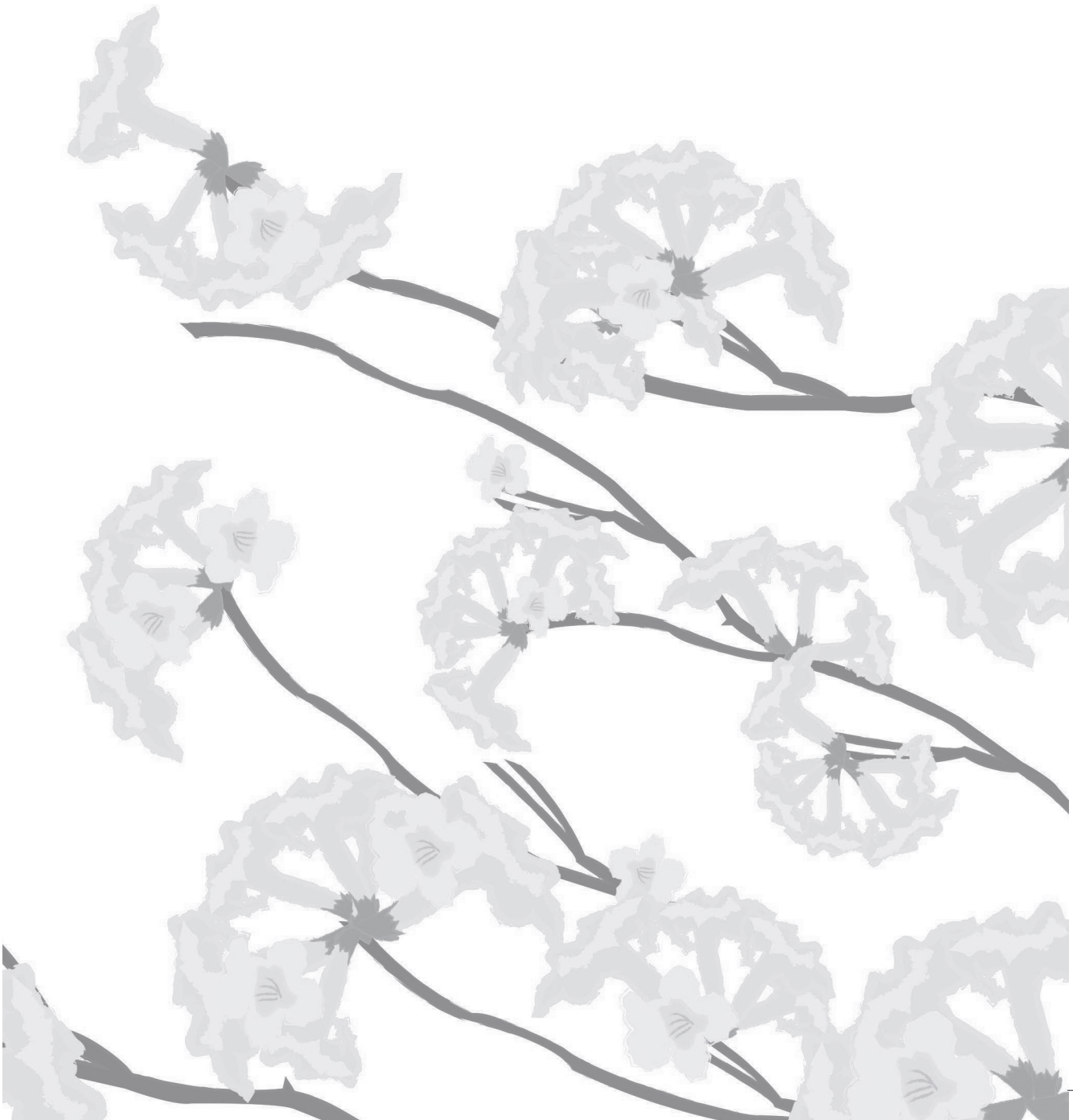
Contents

Chapter 1.	General introduction and thesis outline	7
Chapter 2.	Prevalence of extracranial carotid aneurysms in patients with an intracranial aneurysm PLoS One. 2017 Nov 13;12(11): e0187479. doi: .1371/journal.pone.0187479	13
Chapter 3.	Screening for extracranial carotid artery aneurysms in patients with an intracranial aneurysm In preparation for submission	27
Chapter 4.	Adventitial nerve fiber density in extracranial carotid artery and popliteal aneurysms Submitted	41
Chapter 5.	Gadolinium enhancement and white matter lesions in extracranial carotid artery aneurysms In preparation for submission	65
Chapter 6.	Standardization of semiautomatic tortuosity measurements in the carotid artery Submitted	79
Chapter 7.	Experience of a single center in the conservative approach of 20 consecutive cases of asymptomatic extracranial carotid artery aneurysms. Eur J Neurol 2018 Jun 14. doi: 10.1111/ene. 13720. [Epub ahead of print]	101

Chapter 8.	Treatment of extracranial carotid artery aneurysm: a review of the literature In preparation for submission	115
Chapter 9.	Which carotid aneurysm needs to be treated (and how?) J Cardiovasc Surg (Torino).2016 Apr; 57(2):152-7	159
Chapter 10.	Summary and General discussion	175
Chapter 11.	Nederlandse samenvatting	183
Chapter 12.	Review committee Acknowledgments – Dankwoord List of publications Curriculum Vitae	191

Chapter 1

General introduction and thesis outline



Extracranial carotid artery aneurysms (ECAA) are aneurysms located anywhere between the common carotid artery (CCA) origin at the aortic arch, the cervical part of the external carotid artery and the internal carotid artery till the skull base. An ECAA can have a fusiform shape and is defined as a dilation of the carotid artery of 150% or more, or a saccular shape of any size.[1] The normal diameter of the CCA ranges between 6mm in women to 6.5mm in men, of the ICA from 4.5mm in women to 5mm in men.[2]

Although rare, ECAA can have serious morbidity. Ischemic cerebrovascular accident (iCVA) due to thrombo-embolism is the most feared complication. Other symptoms include cranial nerve dysfunction due to local cervical compression.[1,3-4] However so far, most ECAAs are coincidental findings and are asymptomatic. The outcome of ECAAs if left untreated is still unknown. Conservative, surgical of endovascular treatments have all been reported, but the knowledge is based on a few case series and case reports (this thesis: Chapter 8).[5]

As compared to patients with atherosclerotic carotid artery disease, ECAA patients are in general relatively young with an average age of 55 years at time of diagnosis.[3,6] Therefore, understanding the etiology, the natural clinical course and which ECAA should be treated is important. For this reason, in 2014, the department of vascular surgery started the initiative to raise an international web-based registry on patients with an ECAA and either an asymptomatic or symptomatic ECAA. Currently, over 350 patients have been included and the focus of the registry is now to increase inclusions, collect data on follow up including high quality imaging data. Further, in March 2018 the Department started the option to collect and store blood samples in an ECAA biobank in close collaboration to the Athero-Express vascular biobank. Since 2018, the UMC Utrecht has been recognized as Center of Expertise for patients with ECAA.

General aims of this thesis

The aim of this thesis was to gain more insight in the etiology of ECAA and its natural clinical course. Also, to report on the current knowledge and trends in the treatment of ECAA.

Thesis outline

This thesis will start by describing the prevalence of ECAA in patient with an intracranial aneurysm (IA) in a Dutch (**Chapter 2**) and a Finnish cohort (**Chapter 3**). In chapter 4 the role of the autonomic nerve system on inflammation and the changes in innervation of the vessel wall is assessed and compared to popliteal aneurysms, control healthy carotid and popliteal arteries. Gadolinium enhancement has been described as marker for inflammation.[7] Therefore, in **Chapter 5** the vessel wall and potential inflammation are further explored using MRA with gadolinium, to assess vessel wall enhancement. Also, the presence of cerebral white matter lesions (WML) was explored. WML are associated with stenotic carotid artery are caused by micro-embolic events and are considered markers for cerebral tissue damage, increased stroke risk and cognitive decline over time.[8]

Chapter 6 describes the tortuosity of carotid arteries and its possible link with ECAA development. For the tortuosity measurements different available software packages were compared to test the inter-and intra-observer reproducibility.

Chapter 7 describes the outcome of conservative management of ECAA in our vascular tertiary referral center. **Chapter 8** reports the results of a systematic review that was performed to summarize all the available data on the treatment of ECAA. **Chapter 9** describes all the treatment options for ECAA,

how and when to choose which treatment. **Chapter 10** concludes the thesis with a general discussion and future perspectives.

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Chapter 2

Prevalence of extracranial carotid artery aneurysms in patients with an intracranial aneurysm

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ABSTRACT

Background and purpose: Aneurysms in various arterial beds have common risk- and genetic factors. Data on the correlation of extracranial carotid artery aneurysms (ECAA) with aneurysms in other vascular territories are lacking. We aimed to investigate the prevalence of ECAA in patients with an intracranial aneurysm (IA).

Methods: We used prospectively collected databases of consecutive patients registered at the University Medical Center Utrecht with an unruptured intracranial aneurysm (UIA) or aneurysmal Subarachnoid hemorrhage (SAH). The medical files of patients included in both databases were screened for availability of radiological reports, imaging of the brain and of the cervical carotid arteries. All available radiological images were then reviewed primarily for the presence of an ECAA and secondarily for an extradural/cavernous carotid or vertebral artery aneurysm. An ECAA was defined as a fusiform dilation ≥150% of the normal internal or common carotid artery or a saccular distention of any size.

Results: We screened 4465 patient records (SAH-database n=3416, UIA database n=1049), of which 2931 had radiological images of the carotid arteries available. An ECAA was identified in 12/638 patients (1.9%; 95% CI 1.1-3.3) with completely imaged carotid arteries and in 15/2293 patients (0.7%; 95% CI 0.4-1.1) with partially depicted carotid arteries. Seven out of 27 patients had an additional extradural (cavernous or vertebral artery) aneurysm.

Conclusions: This comprehensive study suggests a prevalence for ECAA of approximately 2% of patients with an IA. The rarity of the disease makes screening unnecessary so far. Future registry studies should study the factors associated with IA and ECAA to estimate the prevalence of ECAA in these young patients more accurately.

INTRODUCTION

Extracranial carotid artery aneurysm (ECAA) is rare and accounts for less than 1% of all peripheral artery aneurysms.[1-3] An extracranial carotid artery aneurysm is defined as a dilation of 150% or more of the diameter of the expected normal carotid artery.[4] Extracranial carotid artery includes the common carotid artery, the external carotid artery and the internal carotid artery (ICA) till the skull base. ECAAs are mostly incidental findings, commonly asymptomatic, and often identified in the ICA. [5]

Aneurysms in general are known to have common risk- and genetic factors and co-occurrences have been described in other arterial beds.[6] Due to the rarity of ECAAs it is unknown what the incidence, prevalence, association with aneurysms in other vascular territories and best treatment approach is.[7] As far as we know, an analysis for correlation between ECAA and IA has not been systematically performed before.

Datasets of patients with an intracranial aneurysm (IA) are available in our center. Therefore, we had the opportunity to investigate the prevalence of ECAA in patients with an IA.

METHODS

Patient selection

We performed a retrospective study in two prospectively collected databases of consecutive patients with an IA admitted to or seen at the outpatient clinic of the Department of Neurology and Neurosurgery of the University Medical Center Utrecht, the Netherlands. Approval was obtained from the Institutional Research Ethics Board. Patients were included from 1978 to 2015 in these datasets. Patients provided informed consent for the use of their medical records for research purposes. One database included consecutive patients with

subarachnoid hemorrhage (SAH), and one with unruptured intracranial aneurysms (UIA). Duplicates between the datasets were removed (i.e. patients in the UIA database with a ruptured IA during follow up). Patients were also excluded if no IA was present, for example if SAH resulted from trauma, an arteriovenous malformation, dural fistula, dissection without an aneurysm or peri-mesencephalic hemorrhage.

Two authors (VP, CL) screened the medical records of all patients in both datasets for available radiological imaging. Then, all original imaging (computed tomography angiography (CTA), magnetic resonance angiography (MRA), digital subtraction angiography (DSA), or duplex ultrasound (DUS) was reviewed for the presence of an ECAA. The available CTA evaluation was on 64-section CT scanners and MRA by the use of 1.5Tesla or 3Tesla scanners. Disagreements were discussed with a third independent observer (GB) until a final agreement was reached. Imaged carotid arteries were categorized into completely or partially depicted. Completely imaged carotid arteries were defined as images starting from the aortic arch until and/or beyond the skull base, depicting both the common, internal as well as the external carotid artery. Carotid arteries were considered partially imaged when either side of the internal carotid arteries was completely depicted (i.e. DSA), or when only the distal carotid arteries were depicted until the second cervical vertebra (i.e. CTA Brain).

Data collection

The diagnosis of an ECAA was determined according to previous radiology reports and by reviewing the available imaging scans of each patient. An ECAA was defined as a dilation of the arterial diameter of ≥150% compared with the normal carotid artery diameter. The side (left versus right, or bilateral), site (common, internal or external carotid artery), shape (saccular, fusiform) and diameter of the aneurysm were retrieved from available reports and by

evaluation of the available images by the authors (VP, CL) independently. In addition to the presence of an ECAA, data on other extracranial/extradural cervical arterial aneurysms were collected and: age at presentation, sex, medical history (diabetes, cardiovascular disease, connective tissue disease, polycystic kidney disease), smoking history, medication and clinical presentation.

Statistical analysis

For continuous variables, we calculated means with standard deviations or medians with ranges. For categorical variables, absolute numbers and/or proportions were calculated with 95% confidence intervals (CI). We calculated the proportion of patients with an ECAA in the complete and partially depicted carotid artery groups.

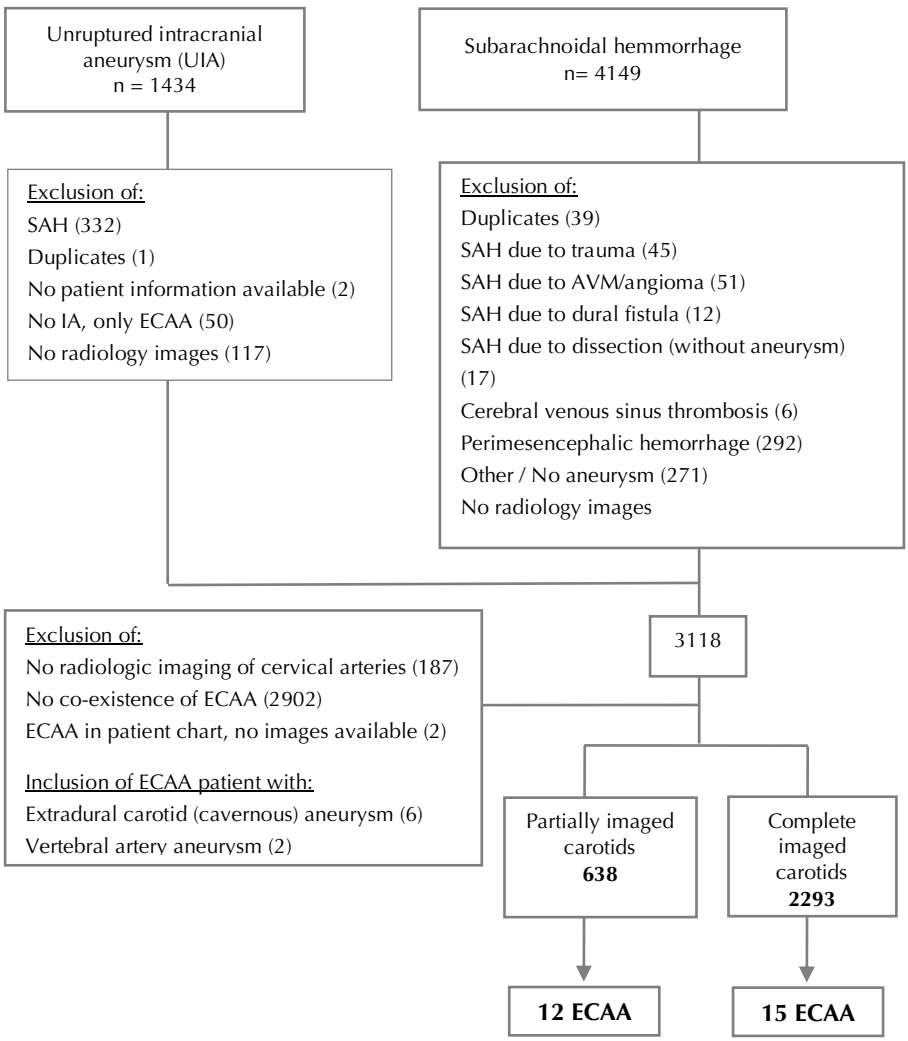
RESULTS

Patients and imaging

After screening both the databases a total of 3118 (70%) patients remained. Of these patients, 638 (20%) had completely depicted and 2293 (74%) partially depicted carotid arteries (Figure 1). The remaining 187 patients (6%) only had a CT or MRI of the brain without the extracranial cervical arteries being depicted. The available imaging modalities of the cervical arteries were CTA, MRA, DSA, and DUS (Table 1). Imaging of a patient with an ECAA is illustrated in figure 2. An ECAA was identified in 12 of 638 patients (1.9%; 95% CI 1.1-3.3) with complete imaging of the carotid arteries, and in 15 of 2291 patients (0.7%; 95% CI 0.4-1.1) with partial imaging. Seven of the 27 patients (26%) with an ECAA had an additional extradural aneurysm (cavernous or vertebral artery). In 17 of the 27 (63%) patients the IA and ECAA diagnosis was made simultaneously. In one patient the ECAA was diagnosed 3.7 years prior to the IA, in nine patients

the IA was diagnosed prior to the ECAA because no imaging of the carotids was performed or available before.

Figure 1. Flowchart of 27 index patients with an IA and ECAA, CA and/or VA.



N = number of patients, UIA = non-ruptured intracranial aneurysm, SAH = subarachnoid hemorrhage, AVM = arteriovenous malformation, IA = intracranial aneurysm, ECAA = extracranial carotid aneurysm, CA = extradural cavernous carotid aneurysm, VA = extracranial vertebral aneurysm.

Table 1. Available radiologic imaging modality of 3118 patients.

		n	Percentage (%)
Imaging of cervical arteries			
	No angiography	187	6
	Partially imaged carotid artery	2293	74
	CTA brain	1134	36)
	MRA brain	214	(7)
	DSA brain	941	(30)
	DUS carotids	4	(<1)
	Completely imaged carotid artery	638	(20)
	CTA carotids	310	(10)
	MRA carotids	118	(4)
	DSA carotids	18	(<1)
	DUS carotids	190	(6)
Diagnosis time interval			
	Intra- and extradural simultaneously	17	63
	ECAA prior to IA	1	(4)
	IA prior to ECAA	9	(33)
	Time, median (y)	8.9	(3.4-23)

Data in n = number of patients (%). Median, range (y) in years.
CTA = computed tomography angiography, MRA = magnetic resonance angiography, DSA = digital subtraction angiography, DSA= digital subtraction angiography, ECAA = extracranial carotid artery aneurysm,
IA = intracranial aneurysm.

Patient characteristics

Characteristics of the patients with an ECAA are presented in Table 2. The median age was 55 years (31-85). Fifteen patients (56%) were women. Of all the patients with an ECAA, 24 (89%) had no symptoms associated with the ECAA.

Table 2. Characteristics of 27 patients with an ECAA

			n	Percentage (%)
Women			15	56
Medical history				
	Diabetes		1	4
	Vascular		12	44
	TIA/Ischemic stroke		5	19
	Connective tissue disorder		2	7
	Trauma in cervical region		0	0
	Polycystic kidney disease		1	4
Smoking history				
	Never		7	26
	Quit smoking		7	26
	Current smoker		9	33
	Unknown		4	15
Medication use				
	None		12	4
	Anti-hypertensive drugs		9	33
	Anti-thrombotic drugs		5	19
		Mono-therapy	4	15
		Multiple-therapy	1	4
	Lipid-lowering drugs		3	11
	Unknown		3	11
Family history				
	Aneurysm		2	7
	Cardiovascular		8	30
	CTD		0	0
	PCKD		1	4
	Unknown		8	27
Clinical presentation				
	Asymptomatic		24	89
	Ipsilateral ischemic stroke		1	4
	Horner's syndrome		1	4
	Local pain		1	4

N = Number. of patients. ECAA = extracranial carotid aneurysm
CTD= connective tissue disease, PCKD= Polycystic kidney disease

Aneurysm characteristics

Aneurysm characteristics are summarized in Table 3. All ECAAs were located in the internal carotid artery. The shape of the ECAA was saccular (n=17) or fusiform (n=17). The median size of the saccular ECAA was 8.0 mm (range 4-13 mm) and for fusiform ECAA 9.0 mm (range 6-12.5 mm). The etiology was mainly unknown, in five cases it was due to dissection, based on radiology images (visible flap) and in one patient due to connective tissue disorder, namely Ehlers-Danlos type IV.

Table 3. Aneurysm characteristics

		IA, n	Percentage (%)	ECAA, n	Percentage (%)
Ruptured		17	63	0	
Side					
	Left	6	16	8	30
	Right	10	26	12	44
	Bilateral	11	58	7	26
Site					
	CCA			0	
	ECA			0	
	ICA			34	100
	Extradural cavernous carotid artery			6 [a]	
	Extracranial vertebral artery			2 [a]	
Shape					
	Saccular			17	50
	Fusiform			17	50
Size in mm, median (range)					
	Saccular			8.4 (4-13)	
	Fusiform			9.2 (6-12.5)	
Presumed etiology					
	Dissection			5	15
	CTD			2	6
	Not reported			28	79

Data in: n= number of aneurysms. [a]Patients with additional extradural cavernous carotid and vertebral artery aneurysm, not included in analysis.
IA = intracranial aneurysm, ECAA = extracranial carotid aneurysm, CCA = common carotid artery, ECA = external carotid artery, ICA = internal carotid artery, CTD = connective tissue disorder.

DISCUSSION

The present study shows that approximately 2% of the patients with an IA and completely imaged carotid arteries has an ECAA. No studies systematically investigated the prevalence of IA and ECAA before.[6] This prevalence could be an underestimation due to heterogeneity of the imaging modalities. In some patients DUS was used, but this modality is operator dependent and it cannot accurately detect distal extracranial carotid aneurysms.[8]

It remains unclear if IAs and ECAAs share the same etiology in the same patients. IAs are mostly saccular shaped,[9] while ECAAs have so far been described to be almost equally divided fusiform and saccular shaped.[4] Also, the wall structure of intracranial and extracranial vessels differs, which may indicate a different pathophysiology.[10] Contrary to IAs, atherosclerosis and dissection has been described as a main cause of ECAAs.[4,11-13]

All identified ECAAs were located in the internal carotid artery; these would be classified as Attigah type I or III, these are aneurysms that involve the ICA.[14] This is in accordance to our not yet published prospective clinical data from an ongoing web-based registry (www.carotidaneurysmregistry.com).[13,15]

CONCLUSION

This is the first prevalence study of ECAA in patients with an IA. In this single-center, retrospective study we found a prevalence of 1.9%. This prevalence indicates the possible rarity of the disease for which screening has not been indicated so far. However, the sparse knowledge on optimal work-up of ECAA is in contrast with the interest in management and long-term clinical outcome of relatively young patients, if left untreated. Future registry studies may elucidate the factors leading to co-existence of both IA and ECAA and estimate the prevalence of ECAA in patients with an IA more accurately.

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Chapter 3

Screening for extracranial carotid artery aneurysms in patients with an intracranial aneurysm

In preparation for submission

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ABSTRACT

Background: The prevalence of extracranial carotid artery aneurysms (ECAAs) in patients with intracranial aneurysms (IAs) was two percent in a Dutch cohort, but heterogeneous and sub-optimal imaging might have led to an underestimation. In this study, we investigated ECAA prevalence in a dataset with complete versus incomplete imaging of the cerebrovascular tree.

Methods: All patients with either a ruptured or unruptured IA within the prospective database of the Department of Neurosurgery, Kuopio University Hospital, Kuopio, Finland were eligible for the present study. All available radiological imaging was reviewed for presence of IA and ECAA. Cerebrovascular imaging was defined as complete (aortic arch to top of the brain, or incomplete (carotid artery depicted only one-sided or from above the carotid bifurcation. ECAA was defined as a fusiform dilation ≥150% compared to the non-affected carotid artery, or a saccular dilation of any size. Prevalences were analyzed by use of χ^2 test, p-value < 0.05 was considered significant.

Results: After screening 1,159 patient records, 463 (40%) had complete imaging, leading to the identification of 24 ECAAs in 21 patients (prevalence 4.5%, 95% CI [0.03;0.07]). An ECAA was identified in 12/696 patients with incomplete imaging (prevalence 1.7%, 95% CI [0.01;0.03]), which was lower compared to the group with complete imaging (p = 0.005).

Conclusion: The prevalence of ECAA in IA patients differs a factor three depending on the extensiveness of the applied cerebrovascular imaging. Therefore, we propose to perform complete carotid imaging in IA patients as the golden standard technique to identify ECAA in these relatively young affected patients for optimal clinical information.

INTRODUCTION

Extracranial carotid artery aneurysm (ECAA) is a rare vascular pathology that accounts for less than 1% of all peripheral artery aneurysms[1-4]. Although ECAAs are rare and mostly coincidental findings, they may cause serious events. The most feared outcome of these aneurysms are ischemic strokes due to thrombo-embolism, or by cranial nerve dysfunction due to local cervical compression.[4-6] As compared to patients with atherosclerotic carotid artery disease, ECAA patients are in general relatively young with an average age of 55 years at time of diagnosis. [1,5,7]

Peripheral aneurysms share several risk and genetic factors, suggesting that the prevalence of ECAA might be high in specific cohorts of patients with more common aneurysms, like intracranial aneurysms (IA).[8-13] However, the prevalence of ECAA in IA cohorts is largely unclear.

We recently reported a prevalence of under two percent of ECAAs in a selected Dutch IA cohort.[1] In that study, the applied radiologic imaging was non-standardized and heterogeneous with most of the carotids incompletely imaged. This might have led to an underestimation of the true ECAA prevalence in IA patients. To confirm and validate the prevalence of ECAA in IA, we studied another European IA cohort operating with a scanning protocol since 2007 including standard imaging from the aortic arch up to top of the skull base by computed tomography angiography (CTA) or magnetic resonance angiography (MRA). The aim of the present study was to evaluate the prevalence of ECAA in another patient cohort with an IA and partially or completely imaged carotid arteries.

METHODS

Patient population

Following Institutional Research Ethics Board approval for this retrospective study, we collected data from the prospective KUH IA database (http://www.kuopioneurosurgery.fi/database) with consecutive IA patients admitted to the KUH, Kuopio, Finland. The KUH is the sole provider of neurosurgical services in its geographical catchment area (approximately 850,000 inhabitants) allowing prospective collection of a population-based IA cohort. Between January 2010 and December 2016, patients aged 18 years or older and with a radiologically confirmed IA were included. Exclusion criteria were: no extracranial carotid arterial imaging available, IAs caused by a trauma, arteriovenous malformation, cavernous malformation, dural fistula or cerebral venous sinus thrombosis.

Data collection

Available cerebrovascular imaging was categorized as complete and incomplete imaging. Complete imaging of the cerebrovascular tree was defined as imaging from aortic arch up to top of the skull base, depicting the common, internal, external and intracranial carotid arteries (i.e. CTA Stroke or carotids). Cerebrovascular arterial imaging was considered incomplete when either only one side of the carotid artery was depicted, or the imaging included only a distal part of the external and internal carotid artery (ICA). Patients undergoing CTA evaluation were scanned with 64-slice CT scanners, MRA imaging was performed on 1.5 Tesla or 3 Tesla scanners. All digital subtraction angiography angiographies (DSA) were reviewed on Sectra AB/PACS Software (Linköping, Sweden).

The diagnosis of IA was determined according to KUH IA database records. The diagnosis of ECAA was determined by reviewing the original radiology

reports and the available radiological images of each patient. Fusiform or spindle-shaped ECAA was defined as ≥150% dilation of the arterial diameter, compared with the non-affected contralateral carotid artery diameter. In case of bilateral dilatation, the diameter of the non-affected part of the ipsilateral carotid artery was used as comparison. For saccular shaped ECAA, all sizes were accepted. Proximally located ECAA in the ICA were defined as located near the bifurcation and distally located was defined and closer to the skull base. The side (left or right), arterial site, shape and diameter of ECAA were retrieved from available radiological reports. In case the size was not reported, two authors (CL, AL) independently measured the maximum aneurysm diameter on available examinations. Disagreements were discussed with an experienced third and fourth independent observer (VP, GB) until final agreement was reached.

Statistical Analysis

Continuous variables are described as mean and standard deviations or medians and ranges, for categorical variables as frequency in percentages. Categorical variables were compared with a χ^2 test. All statistical analyses were performed using SPSS software version 24.0 for Windows (SPSS Inc, Chicago, Illinois, USA).

RESULTS

In total 1,211 patients were available from the KUH IA database. After exclusion of patients without available cervical imaging (n = 40), absence of intradural aneurysms (n = 8), AVM related IA (n = 3) and one duplicate, 1,159 patients remained for analysis (see Figure 1). In 463 (40%) patients, the cerebrovascular tree was completely imaged, while 696 (60%) patients had

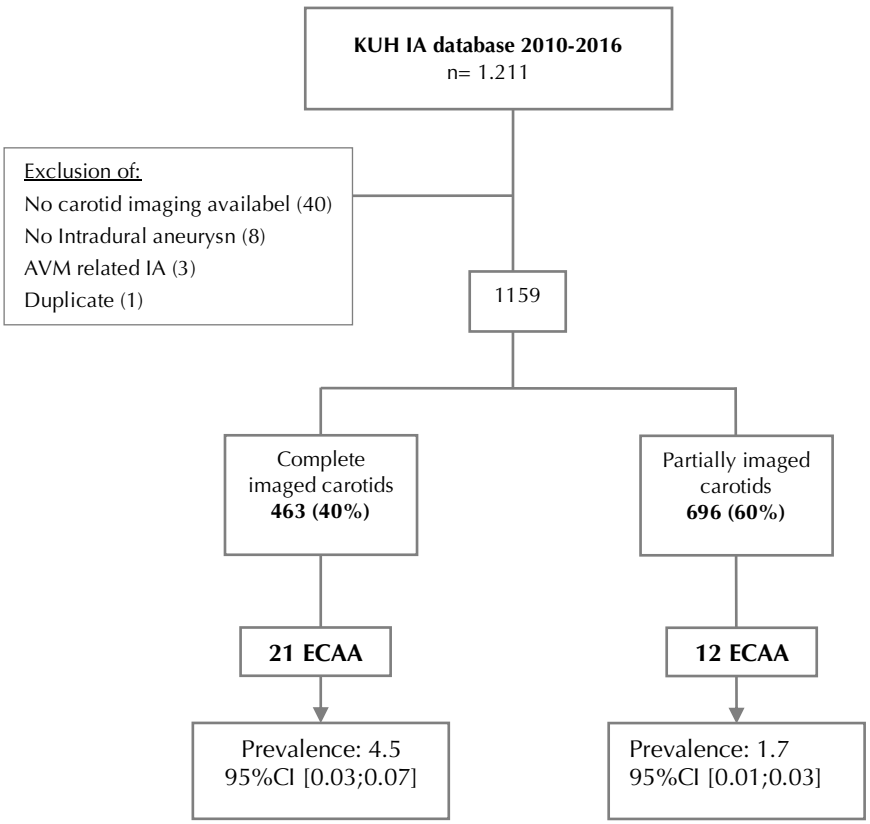
incomplete imaging. For the complete imaging group, the used modality was in 410 (89%) patients CTA, in 29 (6%) MRA, and in 24 (5%) DSA. For the incompletely imaged group, the imaging modality was CTA in 348 (50%) patients, MRA in 295 (42%), and DSA in 53 (8%) patients.

In total, we identified 36 ECAAs in 33 IA patients. Patient characteristics are described in Table 1 and aneurysm characteristics in Table 2. All ECAAs were located in the internal carotid artery. Twenty-seven (75%) aneurysms were located in the distal part, four in the proximal part (13%), and five (14%) affecting the carotid bifurcation. In two patients, ECAAs were found bilateral.

Examples of identified patients are shown in Figure 2 and 3.

In the complete imaging group, 24 ECAAs in 21 patients were identified, which corresponds with a prevalence of 4.5% (21/463), 95% CI [0.03;0.07]. In the incompletely imaged group, 12 patients with an ECAA were identified, resulting in a prevalence of 1.7% (12/696), 95% CI [0.01;0.03]. The prevalence was higher in the patients with complete imaging of the cerebrovascular tree ($p = 0.005$). The prevalence of 4.5% was also higher than the found prevalence of completely imaged patients of the Dutch cohort ($p = 0.011$), see Table 3.

Figure 1. Flowchart of the 33 found IA patients with in total 36 ECAAs



KUH = Kuopio University Hospital, IA = intracranial aneurysm, n = number of patients, AVM = arteriovenous malformation, ECAA = extracranial carotid artery aneurysm, CI = confidence interval.

Table 1. Characteristics of 33 identified ECAA patients

			No.	(%)
Age at presentation, mean (range)			61	(30-80)
Male			18	(55)
Medical history				
	Atherosclerosis		2	(6)
	Cardiac		6	(18)
	Diabetes		3	(9)
	Hypertension		13	(39)
		Not reported	1	(3)
	Respiratory		2	(6)
	Ipsilateral ischemic stroke / TIA		2	(6)
	ADPKD		0	
	FMD		1	(3)
Smoking history				
	Never		7	(21)
	Former		3	(9)
	Current		13	(39)
	Not reported		10	(30)
Family history				
	sIA		2	(6)
	Cardiovascular		NA	
	ADPKD		NA	
	Any CTD		NA	
Intracranial aneurysm				
	Total number		46	
	Patients multiple IA		6	(18)
	Saccular shaped		43	(93)
Clinical presentation of IA				
	Asymptomatic – incidental		16	(49)
	SAH		14	(42)
	Mass		2	(6)
	Not reported		1	(3)

Number of patients (%) unless otherwise indicated. Median, (range) in years.
ECAA = extracranial carotid artery aneurysm, TIA = transient ischemic attack, ADPKD = autosomal dominant polycystic kidney disease, FMD = fibromuscular dysplasia, CTD = connective tissue disease, sIA = saccular intracranial aneurysm, SAH = subarachnoid hemorrhage.

Table 3. Prevalence of ECAA in IA cohorts

Finnish cohort	ECAA (%)	No. ECAA	Total number of scans	p
Complete	21 (4.5)	442	463	
Incomplete	12 (1.7)	684	696	
			1159	0.005*
Validation, complete imaging data				
Finish cohort	21 (4.5)	442	463	
Dutch cohort	12 (1.9)	626	638	0.011*
Groups were compared using χ test, $p < 0.05$ was considered significant. * No.= number				

DISCUSSION

This study shows that 25% percent of the ECAAs in our cohort were located in the proximal part of the carotid artery and the carotid bifurcation. These locations were also reported in the literature.[14] Common and external carotid artery aneurysms locations are rarer then ECAA in the ICA and not observed in our cohort.

Our prevalence of 4.5% in the Finnish validation cohort is higher than in the completely imaged group in the previously reported Dutch cohort.[1] Although we were not able to check possible differences between these IA cohorts, inclusion criteria for the Dutch and Finnish IA database were similar. Also, the type and quality of scanners between both centers are similar since 2007, 64-slice CT (0.67 millimeter per slice) and 1.5T and 3.0T MR scanners, suggesting that more complete imaging of the carotid arteries in the Finnish group, is mostly accountable for the difference.

Peripheral arterial aneurysms have common genetic and vascular risk factors.[8-13] Demographic influences can stimulate these common factors. It is therefore

also possible that demographic factors could influence the higher prevalence of ECAA in the Finnish population.

The present study is limited by its retrospective nature. Due to missing data in medical history, family history and etiology of ECAA. Although aneurysm development shares common genetics and etiologic factors, future research is warranted to understand pathophysiology of concomitant prevalences. We will continue with the prospective ECAA registry (www.carotidaneurysmregistry.com) to compare ECAAs within IA cohorts. Such large-scale comparisons will enable us to detect possible associations between intra- and extracranial aneurysms, and to define an optimal imaging protocol for screening and follow-up.

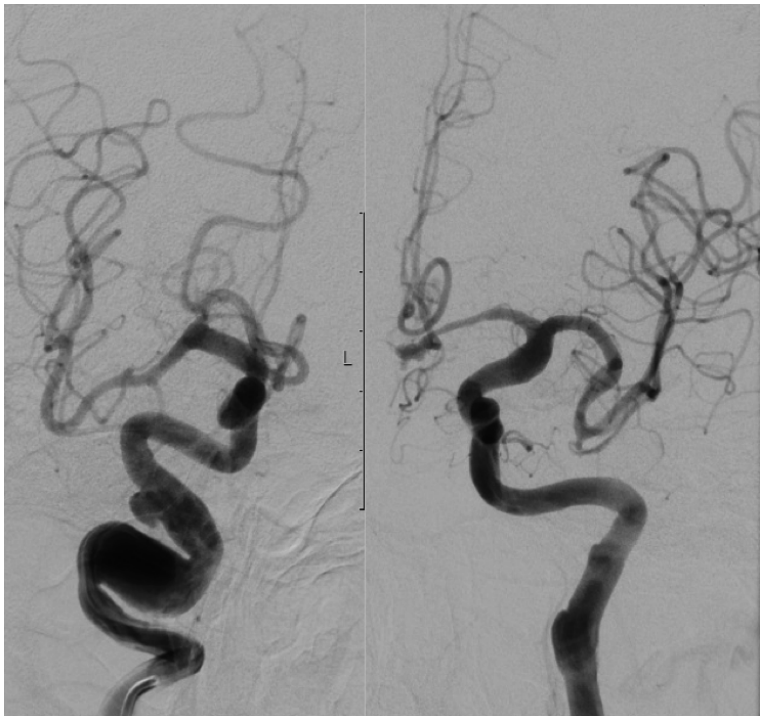


Figure 2. DSA brain of an asymptomatic patient in posterior-anterior configuration.
Left: a fusiform ECAA in the right ICA and saccular shaped ECAA in the distal part of the RICA. Right: a fusiform dilated ECAA in the left ICA and a saccular shaped IA of the anterior communicating artery. Abbreviations: DSA = digital subtraction angiography, ECAA = extracranial carotid artery aneurysm, ICA = internal carotid artery, IA = intracranial aneurysm.

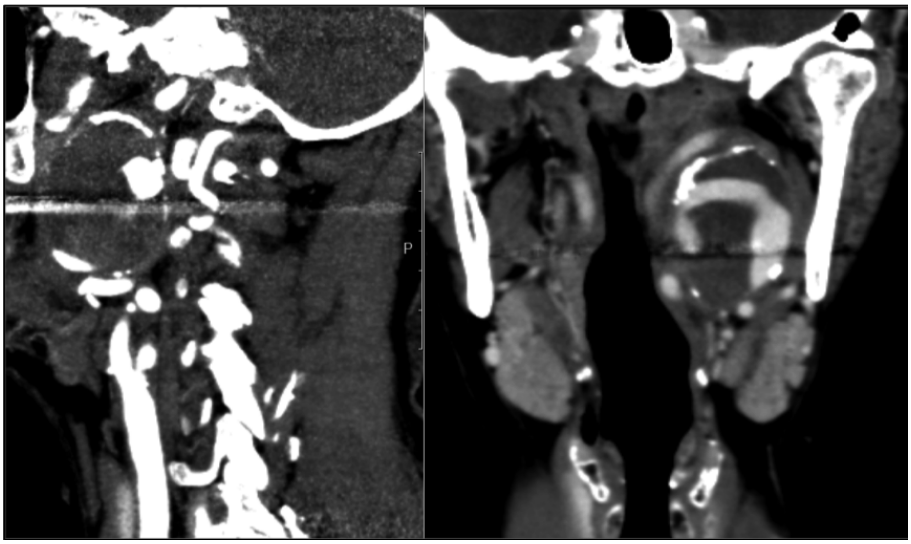


Figure 3. Female patient with history of SAH, presenting with symptoms of voice alterations and dysphagia, CTA showed a giant ECAA in the left ICA.

Left: sagittal view, right: coronal view, both showing a giant ECAA with hyper-dense vessel wall and thrombus within the aneurysm. Artefact by dental implants. Abbreviations: CTA = computed tomography angiography, SAH = subarachnoid hemorrhage, ECAA = extracranial carotid artery aneurysm, ICA = internal carotid artery

CONCLUSION

In this cohort, approximately 1 out of 20 patients had an ECAA. Two-thirds would have been missed if the carotid bifurcation and proximal internal carotid arteries were not imaged. Therefore, we propose to image the complete internal carotid artery including the carotid bifurcation in IA patients as the golden standard technique to identify ECAA in these relatively young affected patients.

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Chapter 4

Adventitial nerve fiber density in extracranial carotid and popliteal aneurysms

Submitted

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ABSTRACT

Objectives: Extracranial carotid artery aneurysm (ECAA) and popliteal artery aneurysm (PAA) are of rare vascular pathology with a heterogeneous etiology and unknown natural course. Arterial wall innervation and especially sympathetic fibers may relate to aneurysmatic growth patterns. The aim of this study was to quantitatively investigate the innervation of ECAAs and PAAs in comparison to non-diseased arteries.

Methods: Carotid (n=10) and popliteal (n=10) aneurysm wall samples of patients that underwent open surgical repair were compared with extracranial carotid (n=6) and popliteal (n=6) control arteries. All tissue samples were immunohistochemically stained for overall nerve fibers (oNF) with anti-protein gene product (PGP) 9.5 and for sympathetic nerve fibers (sNF) with tyrosine hydroxylase (TH). The total stained area was determined for both staining methods. The nerve bundles were counted manually per field of view and recalculated to counts per mm^2. Also, scattered fibers and vasa vasorum associated branches were counted and analyzed as subgroups.

Results: ECAA revealed a non-significant higher number of scattered (sympathetic) fibers in the aneurysmal wall as compared to controls, whereas no difference in oNF density was found. In popliteal arteries, no difference between aneurysms and controls was observed. Nerve density was higher in ECAA as compared to PAA for both oNF and sNF. In control samples, carotid arteries showed higher oNF and sNF density than popliteal arteries.

Conclusions: ECAA showed higher sympathetic nerve densities than popliteal aneurysms, which is in accordance with the topographical differences as found in control arteries. The non-significant increase in scattered nerve fiber density in ECAAs compared to carotid artery control arteries suggests that outgrowth of sNF may be related to aneurysm formation. These observations need to be validated in larger histological samples.

INTRODUCTION

Extracranial carotid artery aneurysm (ECAA) is a rare vascular pathology.[1,2] Although there are no exact data available, the incidence of ECAAs is low. ECAA affects relatively young people around the age of 50 years. An ECAA is generally defined as a dilation in diameter of 150% or more of the carotid artery (CA). It is known that most aneurysms will gradually grow over time and have an increased chance of rupture or in some cases, e.g. popliteal artery aneurysms (PAA) may thrombose and/or result in distal embolization.[3] However, for ECAA this growth pattern and related natural course is still unknown. Therefore, understanding the pathophysiology of aneurysms is important and may provide insights in the natural clinical course. It may also lead to a better treatment approach for these young patients affected.

Different etiologies for ECAA have been described including atherosclerosis, dissection, trauma and infection. Histological analysis revealed dissection and degeneration as the two distinctive underlying mechanisms in ECAA and different inflammatory cells have been observed in the walls of these aneurysms[4]. In addition a decrease in extracellular matrix has been described which, like in abdominal aneurysms, is likely caused by inflammation in the arterial wall.[4,5] Like ECAAs, PAAs are peripheral aneurysms associated with co-presence of other aneurysms (abdominal aorta), but they can also occur in isolation.[6,7] Inflammation has been described in vessel walls of PAA, suggesting a link between arterial wall inflammation and aneurysm formation.[7]

The autonomic nervous system (ANS) has the potential to influence inflammatory responses. The main parasympathetic neurotransmitter acetylcholine has been described to effectively deactivate macrophages, thus inhibiting the inflammatory response.[8,9] Sympathetic influence is found to operate pro- as well as anti-inflammatory.[10] Stimulation of the vagus nerve in animal models and in clinical treatment of rheumatoid arthritis resulted in a

reduction of inflammation.[11–13] Vascular innervation is heterogeneous with respect to location, artery type, nerve fiber density and transmitter content.[14] Moreover local changes of nerve fiber density have been associated with various conditions and diseases including ageing, Alzheimer's disease, peripheral arterial disease, diabetes mellitus and with experimental studies of anosmia.[11,15,16] The above-mentioned factors support the assumption that the ANS plays a role in the inflammatory process, which may be related to vessel wall changes including aneurysmal dilation.

To better understand the role of vessel wall innervation and its influence on ECAA formation, we examined the sympathetic and overall innervation of ECAA and PAA vessel walls. To our knowledge, the innervation of ECAA or any peripheral aneurysm has not been examined before. The aim of this study was to investigate whether there is a quantitative difference in innervation between ECAAs and PAAs as compared to healthy controls.

METHODS

Subjects and sample collection

Ten ECAA samples were available from patients that underwent surgical treatment in two participating hospitals (University Medical Center Utrecht, and St. Antonius hospital, Nieuwegein, the Netherlands) from March 2004 until June 2013. The operation indication for ECAAs was made after multi-disciplinary conference and was based on symptoms, growth and size of the ECAA. All aneurysmal samples were stored in the hospital Biobank and the collection took place under approval of the local medical ethics committees of the two participating hospitals (Verenigde Commissies Mensen Gebonden Onderzoek, St. Antonius Hospital Nieuwegein and Medical Ethical Committee of the University Medical Center Utrecht). All patients provided written informed

consent. To compare ECAAs with other peripheral aneurysms, ten PAA samples, also collected in the hospital Biobank, were analyzed. As controls, six CA and six PA non-aneurysmal samples were extracted from human bodies that entered the department of Anatomy (University Medical Center Utrecht) through a donation program. From these persons written informed consent was obtained during life that allowed the use of their entire bodies for educational and research purposes. Control samples were excised from human bodies preserved in 4% formaldehyde.

All samples were handled according to a standardized protocol.[17] After resection the specimens were fixed in 4% formaldehyde for seven days. Specimens were then decalcified for another seven days in ethylene diamine tetra-acetic acid (EDTA), dehydrated and embedded in paraffin. Subsequently, the samples were cut in 5µm sections and mounted with Entellan (Merck, Whitehouse, NJ, USA).

Immunohistochemical staining

As a standard procedure all sections were treated for antigen retrieval by heating them for 20 minutes in a 95ºC, 0.01M citrate solution with pH=6. Sections were then immunohistochemically (IHC) labeled with polyclonal anti-PGP 9.5 antibodies for staining of any type of nerve fibers (anti Protein Gene Product 9.5, Dako, Glostrup, Denmark, cat.nr: Z5116), or labeled with polyclonal TH-antibodies for sympathetic nerve fibers (anti Tyrosine Hydroxylase, Pel-Freez, Rogers, USA, cat.nr: P40101) and stained with LPR (Liquid Permanent Red, Dako, Glostrup, Denmark, cat.nr: K5355). At 10x magnification on light microscopy, sections were digitized as field of view (0.57x0.87mm) images of the adventitial-medial border with a micro camera (Olympus DP71, associated with Olympus microscope BX53). The number of images depended on the size of the slice and every third picture was used for quantification. All results are recalculated to and presented as counts per square millimeters (mm^2).

Quantification and statistical analysis

PGP 9.5- and TH-immunoreactivity were quantified and expressed as an area percentage of the total standard picture size, using the image analysis software ImageJ[18]. Furthermore, nerve fibers, as clustered in bundles, those in close vicinity of vasa vasorum and scattered nerve fibers were counted manually per field of view and recalculated to counts per mm^2 (Figure 2a-b). Any cluster of nerve fibers, separated from the surrounding tissue by an epineurium, was considered a nerve bundle. All nerve fibers surrounding one particular vessel in the vasa vasorum were counted together as one. Other stained nerve fibers, not in a bundle or near the vasa vasorum, were considered scattered nerve fibers and received one count per ten individual fibers.

Statistical analysis

A nonparametric One-way Anova with an uncorrected Dunn's multiple comparisons test was performed with Prism7 (GraphPad Software, La Jolla California USA, www.graphpad.com) to compare total and sympathetic innervation in healthy and aneurysmal carotid and popliteal arteries. Data are presented as mean and a p-value of <0.05 was considered statistically significant.

Quantification method, by ImageJ as well as manually, was validated by comparing in duplo quantification by two different observers to provide inter- and intra-observer correlations. With power=1.00000 and $\alpha=0.05$, together with a large number of subjects, an intraclass correlation was achieved of 0.80 resulting in an acceptable bias of maximum 5 for area (M=72.8), and max 0.13 for counted fibers (M=1.09) quantification (see appendix 1.)

RESULTS

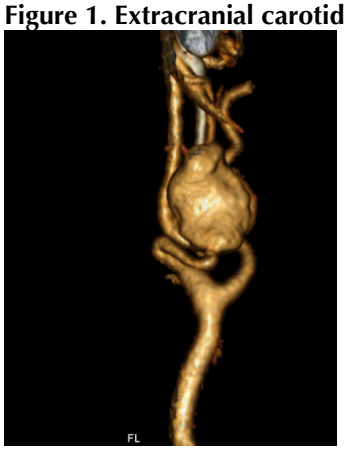
Patient characteristics

The median age of the ECAA patients was 58 years (range 25-76), five were male. Of the ten included ECAA patients, nine were symptomatic. Ten PAA samples were included of nine patients, with a median age of 74 years (range 49-82). Seven patients had a symptomatic PAA. Patient characteristics are presented in table 1.

Aneurysms

Most of the ECAAs were located in the internal CA (n=8, 80%). Of these eight carotid arteries, six were in the distal carotid artery and the other three in the proximal internal CA. An example of an ECAA in the internal CA is shown in Figure 1. The majority of the aneurysms was located on the left side (n=6, 60%). The mean diameter was 12.5mm and 27mm for saccular (n=4) and fusiform aneurysms (n=6) respectively. The presumed etiology of the ECAA was degeneration (n=9) and dissection (n=1). Of the PAAs six out of ten (60%) were located on the right side. The mean diameter of popliteal aneurysm was 32mm. Specimens' characteristics are presented in Table 2.

Figure 1. Extracranial carotid artery aneurysm



Controls

Post-mortem non-aneurysmal carotid specimens from six cadaveric donors with a mean age 89 (range 75-98) and PA samples from six cadaveric donors with a mean age of 73 (range 57-89) were used as controls.

Table 1. Characteristics of ECAA and popliteal aneurysm patients.

	ECAA patients (n= 10)	Popliteal aneurysm patients (n=9)	
Gender male (%)	5 (50)	8 (89)	
Age (mean), years (range)	58 (25-76)	74 (49-82)	
Hypertension (%)	5 (50)	6 (67)	
MI (%)	1 (10)	1 (11)	
COPD (%)	0 (0)	3 (33)	
Statin use (%)	4 (40)	4 (44)	
Connective Tissue disease (%)	0 (0)	0 (0)	
Smoking (currently/past) (%)	3 (30)	2 (22)	
DM (%)	1 (10)	2 (22)	
Symptoms			
ECAA		Popliteal aneurysms	
TIA Stroke Local compression Contralateral symptoms.	3 (30) 1 (10) 1 (10) 4 (40)	Distal embolus Rupture Pain Edema	4 (44) 1 (11) 1 (11) 1 (1)
Data presented as numbers unless otherwise indicated. Abbreviations: MI: Myocardial infarction, COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus. TIA= transient ischemic attack, includes local pain, mass or hoarseness. ECAA= extracranial carotid artery aneurysms			

Table 2. Aneurysm Characteristics

	ECAA (n=10)	Popliteal aneurysms (n=10)
Location	1 Left bifurcation 5 LICA, 3 RICA 1 RCC	6 Right
Shape	4 saccular 6 fusiform	
Size, mean in mm (range)	Saccular: 12.5 (11-15mm) Fusiform: 27 (13-33mm)	32 (8-67mm)
Symptomatic (%)	9 (90)	8 (80) 2 (20) unknown
Data presented as numbers unless otherwise indicated. Abbreviations: ECAA= extracranial carotid artery aneurysms, RCC: right common carotid artery, LICA: left internal carotid artery, RICA: right internal carotid artery		

Innervation density

In the IHC staining method of overall and sympathetic nerve tissue, different antibodies were used. Anti-PGP 9.5 and anti-TH bind to different sites in the tissue and TH stains obviously more intense than PGP 9.5. Consequently, in quantification, TH can present more counts per square millimeter than PGP, which can cause some confusion since the sympathetic nerves are by definition a part of the total innervation. The comparisons in this study were therefore made only between tissues stained in the same batch. Presence of sympathetic fibers was not quantitatively compared with overall nerve counts.

Immunohistochemistry yielded satisfying specific results from PGP 9.5 as well as TH staining procedures. Images were clear and well suited for quantification (Figure 2a-b). Validation of the quantification method resulted in satisfying values (appendix 1).

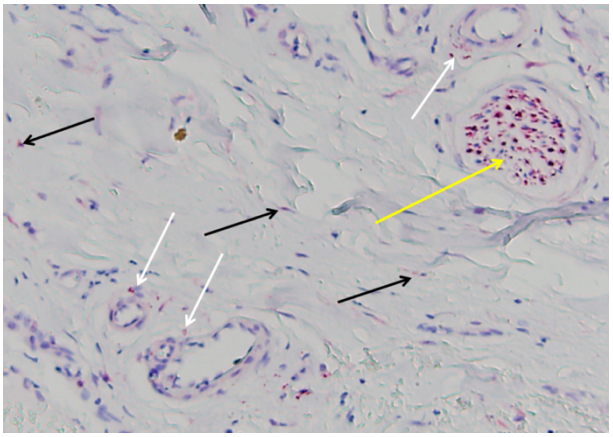


Figure 2A: Histology of a PGP 9.5 stained carotid artery aneurysm.
Yellow arrows: nerve bundle, white: vasa vasorum related fibers,
Black: scattered fibers

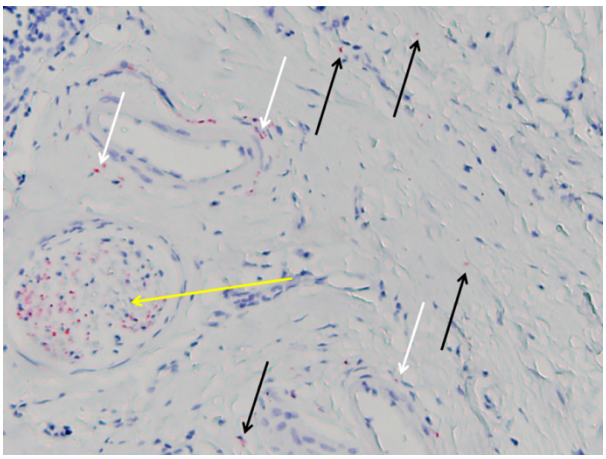


Figure 2B: Histology of a TH stained carotid artery aneurysm.
Yellow arrows: nerve bundle, white: vasa vasorum related fibers, black: scattered fibers

In both CA and PA, no significant difference was observed between aneurysms and control samples for overall PGP and sympathetic TH stained area (fig 2), total number of bundles (Figure 4), vasa vasorum related fibers (Figure 5) and scattered fibers (Figure 6). In CA however, loose scattered oNF (overall nerve

fibers) as well as TH positive sympathetic nerve fibers (sNF) showed an increased density in the aneurysms as compared to controls (PGP 9.5 oNF scattered fibers: Mean control CA 0.93 vs. ECAA 9.19 counts/mm^2, p=0.133 and TH scattered fibers: Mean control CA 0.65 vs. ECAA 5.76 counts/mm^2, p=0.100; fig 5). Further analysis showed a strong correlation between values in oNF and sNF, equally in measured areas and nerve counts (Table 4). High scores of nerve fibers in PGP 9.5 correspond with those in TH stained samples.

In control samples, oNF as well as sNF, was found to be higher in carotid than in popliteal samples. This was significant for total oNF stained area and vasa vasorum associated fibers (oNF area control CA 165.00 vs. control PA 10.70 counts/mm^2, p=0.006 and vasa vasorum associated fibers control CA 0.95 vs. control PA 0.04 counts/mm^2, p=0.013; Figure 3 and 5) and showed a trend for number of sNF bundles (sNF bundles control CA 0.59 vs. control PA 0.03 counts/mm^2, p=0.059; fig 3). This higher nerve density in the carotid compared to the PA was even more pronounced in the aneurysmal groups. In aneurysms, oNF and sNF area (Figure 3), numbers of bundles (Figure 4), and vasa vasorum associated fibers (Figure 5) and scattered fibers (Figure 6) were all significantly higher in ECAAs than in PAAs (Table 3).

Table 3. Means and significance nerve fiber counts

3A. General type nerve fibers					3B. Sympathic nerve fibers			
PGP 9.5	**Control CA mean**	**ECAA mean**	**p**		**TH**	**Control CA mean**	**ECAA mean**	**p**
Area	165	362	0,743		**Area**	37,3	110	0,3644
Bundels	0,40	1,44	0,300		**Bundels**	0,59	0,79	0,667
VV associated	0.95	1,67	0,997		**VV associated**	0,46	1,57	0,213
Scatterd	0,93	9,19	0,133		**Scatterd**	0,65	5,76	0,100
	Control PAA	**PAA**	**p**			**Control PAA**	**PAA**	**p**
Area	10,7	38,9	0,510		**Area**	29,0	20,3	0,510
Bundels	0,03	0,06	0,596		**Bundels**	0,03	0,15	0,404
VV associated	0,04	0,08	0,721		**VV associated**	0,27	0,25	0,765
Scatterd	0,44	0,16	0,633		**Scatterd**	0,52	1,15	0,833
	Control CA	**Control PAA**	**P**			**Control CA**	**Control PAA**	**p**
Area	165	10,7	0,006		**Area**	37,3	29,0	0,721
Bundels	0,40	0,03	0,189		**Bundels**	0,59	0,03	0,059
VV associated	0,95	0,04	0,013		**VV associated**	0,46	0,27	0,401
Scatterd	0,93	0,44	0,197		**Scatterd**	0,65	0,52	0,706
	ECAA	**PAA**	**p**			**ECAA**	**PAA**	**P**
Area	362	38,9	0,03		**Area**	110	20,3	0,023
Bundels	1,44	0,06	0,043		**Bundels**	0,79	0,15	0,048
VV associated	1,67	0,08	0,012		**VV associated**	1,57	0,25	0,004
Scatterd	9,19	0,16	0,00		**Scatterd**	5,76	0,15	0,032

Carotid (ECAA) and popliteal (PAA) aneurysms vs. control arteries. 3a: Total nerve fibers stained with PGP 9.5 3b: Sympathetic type of nerve fibers stained with TH. Abbreviations: VV = vaso vasorum CA= carotid artery

Figure 3. Total and sympathetic innervation measured as areas.

3a **3b**

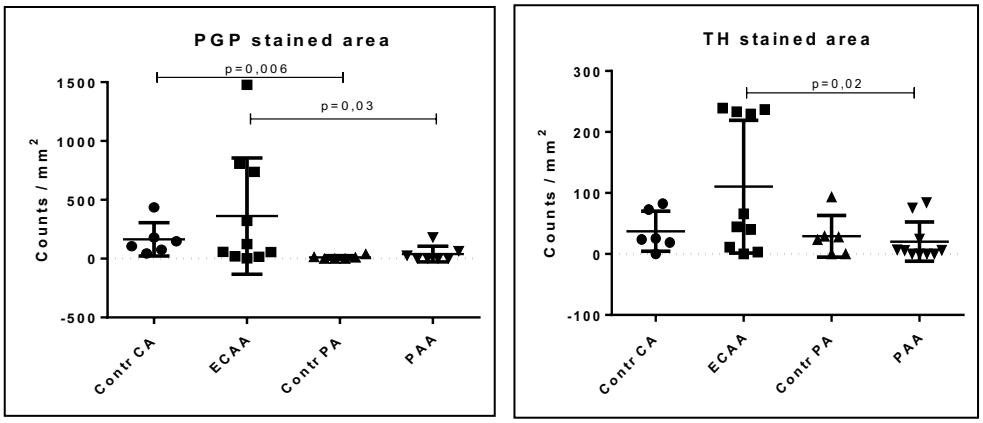
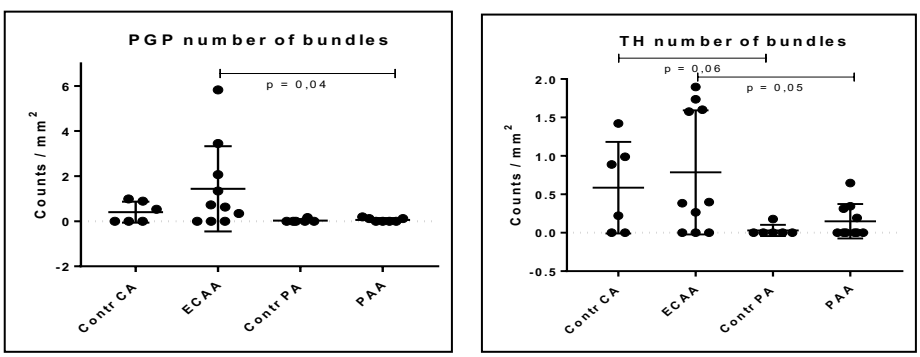


Figure 3: Comparison of (3a) PGP 9.5 stained total innervated area and (3b) TH stained sympathetic area, in stained area per mm², in arteries with and without aneurysm. Groups: Contr. Ca = Control carotid artery (N=6), ECAA= extracranial carotid artery aneurysm (N=10), Contr PA= control popliteal artery (N=6) and PAA= popliteal artery aneurysm (N=10).

Figure 4. Counts of total and sympathetic nerve bundles.

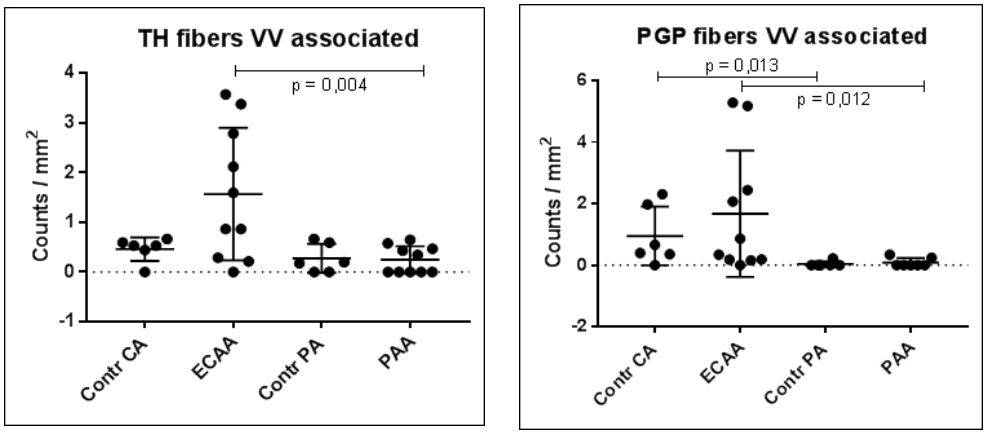
4a **4b**



Comparison of (4a) PGP 9.5 stained numbers of total nerve bundles and (4b) TH stained numbers of sympathetic nerve bundles in arteries with and without aneurysm. Groups: Contr. CA= Control carotid artery (N=6), ECAA= extracranial carotid artery aneurysm (N=10), Contr PA= control popliteal artery (N=6) and PAA= popliteal artery aneurysm (N=10).

Figure 5. Counts of total and sympathetic vasa vasorum associated nerve fibers.

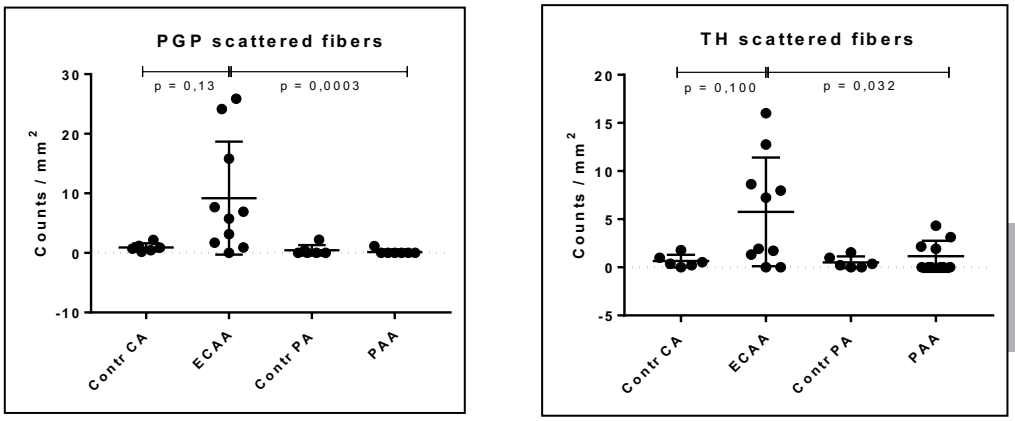
5a **5b**



Comparison of (5a) PGP 9.5 stained total vasa vasorum associated nerve fibers and (5b) TH stained sympathetic v.v. associated fibers in arteries with and without aneurysm. Groups: Contr CA= Control carotid artery (N=6), ECAA= extracranial carotid aneurysm (N=10), Contr PA= control popliteal artery (N=6) and PAA= popliteal artery aneurysm (N=10).

Figure 6. Counts of total and sympathetic scattered nerve fibers.

6a **6b**



Comparison of (6a) PGP 9.5 stained total scattered nerve fibers and (6b) TH stained scattered sympathetic fibers in arteries with and without aneurysm. Groups: Contr CA= Control carotid artery (N=6), ECAA= extracranial carotid artery with aneurysm (N=10), Contr PA= control popliteal artery (N=6) and PAA= popliteal artery aneurysm (N=7).

DISCUSSION

This explorative study has two important results. First, we observed a non-significant higher rate of scattered sympathetic nerve fibers in ECAAs as compared to control CAs. This was observed for both oNF and sNF scattered fibers. Second, a higher nerve density was found in ECAA as compared to PAA samples, but also in carotid controls as compared to popliteal controls. The difference in nerve density was more obvious in the aneurysm groups than between the controls and was found for both overall and sympathetic innervation.

More scattered fibers in ECAAs than in controls could mean that growth of these fibers is drawn to the aneurysmal site. They could fulfill a function in the development of the aneurysm. In other words, that they actively take part in processes, whether or not inflammatory, that weaken the arterial wall or make

an attempt to minimize a primary damage by mechanical or infectious causes. The relation between innervation and inflammation has formerly been described[19–21] and, because of the inflammatory nature of atherosclerotic aneurysms, might provide an explanation for the increased presence of nerve fibers in the aneurysmal arterial wall. The specific innervation in ECAA resulting from carotid dissection could not be studied due to the limited number of ECAA samples available in our biobank.

Preservation

As standard treatment antigen retrieval was executed on all human sections before IHC, which might have restored disturbing changes in tissue structures before the staining procedure.

Location

While ECAAs tend to develop close to the carotid bifurcation, popliteal aneurysm formation is expected to be initiated by vascular injury, most probably caused by mechanical forces following strong bending of the knee. As such, location will be a factor of importance in the initiation of aneurysm formation.
The CA is a resistance artery and especially the internal branch is closely involved in pressure regulation and perfusion of the brain. Neural pressure sensitive receptors in the carotid sinus keep blood pressure and flow to the brain within acceptable range[22]. Baroreceptor tissue has been described to be visible using PGP 9.5 staining and is reportedly to be mostly localized in the medial portion of the proximal ICA.[23] The ECAA we included were mostly (60%) located in the distal CA, while three were located near the bifurcation/proximal CA and one was located in the common carotid artery. This could potentially have influenced the observed nerve density in our ECAA samples, with a relative higher expected nerve density in the samples derived from the more proximal CA.

Inflammation

Results suggest that the increased density of scattered fibers in the CA is in part caused by sympathetic fibers (Table 4). In rodent studies with experimental myocardial infarction (MI), inflammatory cell synthesized Nerve Growth Factor (NGF) leads to sympathetic nerve sprouting in the peri-infarcted area[24,25]. In another study, NGF stimulates nerve growth as well as angiogenesis in and around the injured arterial wall in the mouse[26]. This provides evidence of a simultaneous outgrowth of nerves and blood vessels upon inflammatory cell regulated NGF-release in order to protect damaged tissue[27]. This principle reaction might explain the denser innervation found in diseased vessels and we therefore emphasize further research should be aimed at inflammatory processes in aneurysm development.

Table 4. Correlations PGP 9.5 with TH

Correlation PGP 9.5: TH	
Area	R=0,53
Bundles	R=0,48
VV assoc.	R=0,70
Scattered	R=0,79

Table 4: Correlations between PGP-9.5 (Total innervation) and TH (sympathetic fibers) stained results.Abbreviations: VV = vaso vasorum

Limitations

Due to the rarity of ECAA samples available for histological staining and the limited number of ECAA patients undergoing surgery, the present analysis could only be performed on a small number of cases. In addition, the majority of the selected ECAA patients were symptomatic and had a surgical treatment, thus

the results of this explorative analysis apply to symptomatic ECAA patients that underwent surgery.

The mean age of ECAA was higher in controls and in PAA patients. In intracranial aneurysms an association had been found between age and increased arterial wall innervation.[28] However, there are distinct differences in arterial wall anatomy between intracranial versus extracranial carotid arteries; namely the external carotid artery is considered an elastic artery while the internal carotid artery is considered a muscular artery.[29] The difference between the intracranial portion and the extracranial internal carotid artery is in the vessel wall thickness and lamina elastica externa. The intracranial portion lacks this layer of the elastic lamina and this change occurs in the cavernous portion of the internal carotid artery.[30]

Aneurysm nerve density could also depend on stage of the aneurysm development, age and physical condition of the donor. Furthermore, innervation patterns can only be studied ex vivo and noninvasive imaging techniques will be useful to serve as a diagnostic approach in vessel wall characteristics assessment.

CONCLUSIONS

In this explorative study on a small but unique set of ECAA and PAA arterial wall samples, ECAAs showed a non-significant higher overall nerve density as compared to PAAs. Nerve densities measured as stained area as well as vasa vasorum associated scattered nerve fibers in control CAs showed higher values as compared to those in control PAAs. An increased density of scattered nerve fibers in ECAAs compared to control CAs suggests that outgrowth of small adventitial nerve fibers from pre-existing bundles may be related to aneurysm

formation. The role of innervation in aneurysm growth patterns needs to be validated in larger histological sample sets.

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Chapter 5

Gadolinium enhancement and white matter lesions in extracranial carotid artery aneurysms

Submitted

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ABSTRACT

Background: The exact etiology of extracranial carotid artery aneurysms (ECAA), the growth pattern and cerebrovascular prognosis when treated conservatively are unknown. Gadolinium-enhancement of aneurysm wall has been described as a possible indicator of inflammation which might play a role in aneurysm formation and growth. Carotid artery disease related white matter lesions (WML) are considered markers for cerebral tissue damage and increased stroke risk.

Objective: To determine the presence of gadolinium-enhancement in the vessel wall and the presence of ipsilateral cerebral WML in asymptomatic ECAA undergoing conservative treatment.

Methods: In this feasibility study, vessel wall magnetic resonance angiography (MRA) with gadolinium administration was prospectively performed in 15 patients with 17 ECAAs. Primary endpoints were 1) Arterial wall gadolinium enhancement (single observer) and 2) the presence of WML (two independent observers), scored at two time points. The intra- and interobserver agreement was calculated using Kappa statistics with 95% confidence intervals.

Results: Gadolinium enhancement was observed in 14 of the 17 ECAAs. The intra-observer agreement was excellent for gadolium enhancement with a Kappa of 0.82 (95% CI 0.58-1.1) The presence of ipsilateral WML scored by two radiologists, ranged from 7 to 11 of the 15 patients. The intra-observer agreement for WML ranged from substantial (Kappa 0.70, 95% CI 0.14-0.98) to almost perfect (0.91, 95% CI 0.74-1.0). The inter-observer agreement was moderate (0.45, 95% CI 0.13-0.77).

Conclusion: In this explorative study, arterial wall imaging with MRA revealed gadolinium enhancement in the majority of ECAA and most patients had ipsilateral WML.

INTRODUCTION

The etiology and prognosis of extracranial carotid artery aneurysms (ECAA) remain unclear. Histopathological research revealed dissection and degeneration as the two main causes of ECAA, with the presence of inflammatory cells in the degenerative vessel wall.[1] MRI and histopathological studies on atherosclerotic carotid arteries have suggested that gadolinium enhancement reflects the density of vasa vasorum and inflammation in the arterial wall.[2,3] Also, MRI imaging has been suggested as a non-invasive tool in the early detection of arterial wall changes and may be useful for routine monitoring and evaluation of disease activity.[3] Most ECAAs are coincidental findings and a conservative approach is presently considered justified in patients with asymptomatic ECAA.[4] Several surgical and endovascular techniques have been developed for ECAA exclusion, but these interventions are mostly reserved for patients with neurological symptoms or with proven growth.[5,6] However, the growth pattern and long-term risk of thrombo-embolization and subsequent stroke has yet to be elucidated. Previous studies have shown that patients with carotid stenosis have subclinical microvascular cerebral damage due to micro-embolic events.[7] The presence of white matter lesions (WML) is a sign of micro-embolic events and its presence has been described to be correlated with increased future cerebrovascular risk and cognitive decline over time.[8] Therefore, the challenge is to develop new imaging techniques to determine ECAA disease activity and its effect on the brain to possibly predict future cerebrovascular outcome. In the present explorative study, we aimed to investigate the presence of gadolinium enhancement and the presence of ipsilateral cerebral white matter lesions in patients with an asymptomatic ECAA treated conservatively.

METHODS

This imaging study was conducted after approval of the local medical ethics commission (METC Utrecht). Patients aged >18 years with a conservatively treated ECAA that has been asymptomatic at least 1 year prior to the start of the study and registered in the ECAA registry were eligible for inclusion. Patients planned for a follow up CTA scan of the carotid arteries were approached by the study coordinator for participation. Patients were included after an informed consent form was signed. Patients were included between February and September 2017. Due to the rarity of the disease, no power calculation was performed.

MR imaging

A 3T MRI scanner (Software release 5.3, Philips Healthcare, Eindhoven, the Netherlands) was used for the vessel wall imaging. The MRI imaging protocol consisted of a standard brain imaging series for detection of infarcts. Subsequently, a series of sequences were used before and after gadolinium (Gadobutrol, Bayer Healthcare, Berlin, Germany, 0.1 mmol/kg body weight) injection.

One neuro-radiologist (JH) viewed and scored the MRI scans for gadolinium enhancement. The sequences before and after administration of gadolinium were compared to determine the presence of gadolinium enhancement. A previous study showed that such visual assessment of gadolinium enhancement in intracranial aneurysms have excellent inter- and intra-observer agreement (kappa 0.85; 95% confidence interval (95% CI) and 0.90; 95% CI 0.83-0.98).[9] Aneurysm wall enhancement was considered present if there was a hyperintensity of the wall on the MRI after gadolinium administration, that was not present on the MRI before gadolinium administration. Two experienced neuro-radiologists (JH, TL), blinded for the patient characteristics, aneurysm location and reported shape and size, independently scored two rounds of the MRI images, with a minimum of two weeks between the measurements, scoring the aneurysm size on MRI images.

White matter lesions

The two radiologists also independently scored the MRI images for the presence of white matter lesion (WML). The white matter lesions were determined using the Fazekas rating scale on the fluid attenuated inversion recovery sequence (FLAIR), with Fazekas 0 being no white matter lesions present and 3 being severe peri-ventricular or deep white matter lesions.[10]

Statistical analysis

The intra-observer agreement of gadolinium enhancement was determined using Kappa statistics. A Kappa of 0.81-1.00 equals an almost perfect agreement, a Kappa of 0.61-0.80 a substantial agreement and a Kappa of 0.41-0.60 a moderate agreement.[11] The interclass correlation (ICC) was used to calculate the intra- and inter-observer agreement for the aneurysm diameter. The intra- and inter-observer agreement on WML on the Fazekas scale was calculated with Kappa statistics. The intra- and inter-observer agreement on WML was also calculated using a binary scale, defining WML as present or absent. Analyses were performed using SPSS 22.0 (IBMG. Corp. released 2013. IBM Statistics for Mac, Version 23. Armonk, NY: IBM Corp).

RESULTS

Patients and aneurysms characteristics

Most of the included patients were male (n= 8, 53.3%) with a mean age of 55 years (range 40-71 years). All the ECAA were located in the internal carotid artery. Most aneurysms had a fusiform shape (n=11) and had an unknown (n=7) or dissection (n=6) as a presumed etiology. The patient and aneurysm characteristics are shown in table 1 and 2. The agreement between the diameters measured by the radiologists was nearly perfect with an ICC of 0.99 as summarized in table 2.

Table 1. Patient and aneurysm characteristics

Patient characteristics	**Patients (n=15)**
Mean age	55.5 (range 40-71)
Female sex	7 (47%)
Hypertension	5 (33%)
Smoking	
Current	2 (13%)
Previous	2 (13%)
Never	7 (47%)
Diabetes Mellitus	0
Statin use	3 (20%)
Anti-platelet drugs	7 (47%)
Previous neurological symptoms	
None	5 (33%)
Ipsilateral TIA	2 (13%)
Contralateral TIA	1 (7%)
Ipsilateral **stroke**	3 (20%)
Contralateral **stroke**	1 (7%)
Ipsilateral hemorrhagic stroke	1 (7%)
Horner's syndrome	2 (13%)
Aneurysm characteristics	**ECAA (n=17)**
Fusiform shape	11 (65%)
Right side	9 (53%)
Presumed etiology	
Dissection	6 (40%)
Unknown	7 (47%)
Other[b]	2 (13%)
Mean diameter[c]	14.2 mm

Abbreviations: ECAA= extracranial carotid artery aneurysms.

[a] ischemic stroke

[b] Includes trauma and fibromuscular dysplasia, [c]Calculated using the average measured by both radiologists. Abbreviations: TIA= transient ischemic attack

Table 2. inter- and intra-observer variability of ECAA diameter measurements

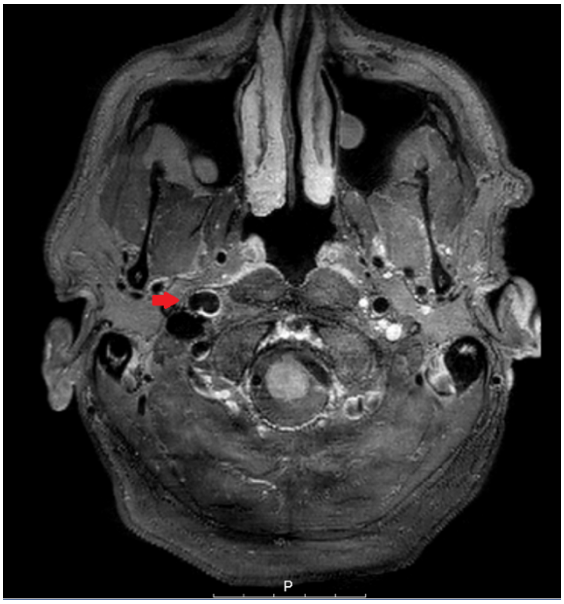
Inter-observer variability	Intra-observer variability (observer 1)	Intra-observer variability (observer 2)	Average intra-observer variability
0.98 (0.95-0.99)	0.98 (0.97-0.99)	0.99 (0.99-1.0)	0.99

Inter-observer variability was calculated using the first round of measurements by both radiologists. The average intra-observer variability was calculated using the average ICC of both radiologists. Values are intraclass coefficient (ICC) with 95% confidence interval (CI). Abbreviations: ECAA= extracranial carotid artery aneurysms

Gadolinium enhancement

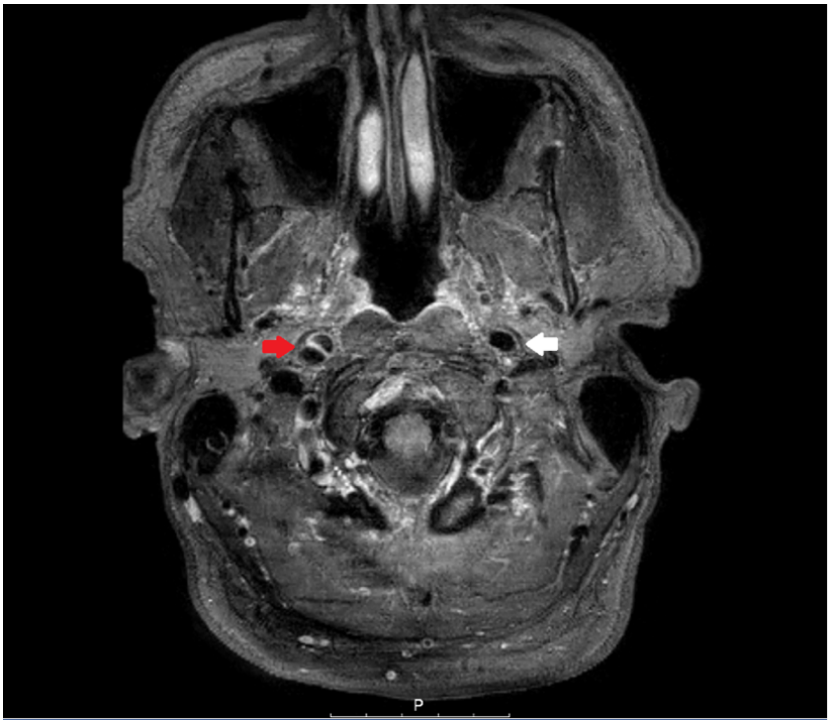
Of the 17 ECAAs, 14 had gadolinium enhancement. The intra-observer variability for gadolinium enhancement was excellent with a Kappa of 0.82 (95% CI: 0.58-1.0). An example of gadolinium enhancement in an ECAA is shown in Figure 1. Three ECAAs had no enhancement and only one these patients had hypertension, used an anti-inflammatory drug (acetylsalicylic acid), statin and had hypertension.

Figure 1. Aneurysm wall enhancement



Example of aneurysm wall enhancement after gadolinium administration on 3T MRI-imaging (red arrow) in a 60-year-old male with a 10mm saccular ECAA.

Figure 2. Unilateral gadolineum wall enhancement



Example of aneurysm wall enhancement after gadolinium administration on 3T MRI-imaging (red arrow) in a 54-year-old male with a 10mm saccular aneurysm on the left, and a fusiform aneurysm without gadolinium enhancement (white arrow) of 7mm on the right side.

White matter lesions

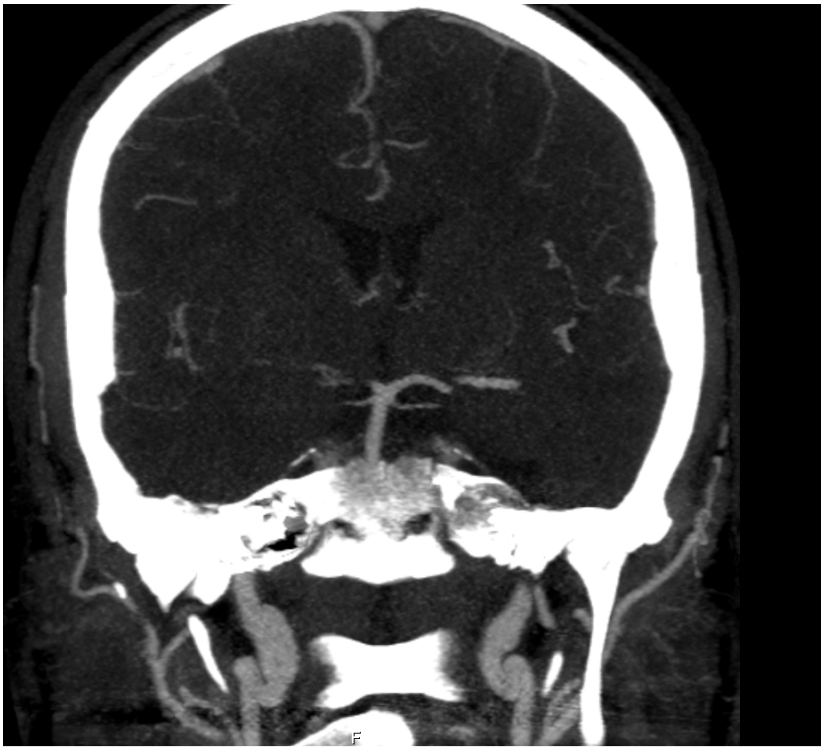
Presence of ipsilateral WML ranged from 7 to 11 of the 15 patients with an ECAA. The intra-observer agreement for WML using the Fazekas scale ranged from substantial to excellent with a Kappa of 0.70 and 0.91, with an average agreement of 0.81 (Table 3). The inter-observer agreement was moderate with a Kappa of 0.46. When using the binary scale, the intra-observer agreement ranged from 0.82-0.87, with an average agreement of 0.84. The inter-observer agreement was moderate with a Kappa 0.59.

Table 3. inter- and intra-observer variability of ipsilateral white matter lesions

Inter-observer variability	Intra-observer variability (observer 1)	Intra-observer variability (observer 2)	Average intra-observer variability
0.46 (0.13-0.77)	0.70 (0.42-0.98)	0.91 (0.74-1.0)	0.81
0.59 (0.21-0.97)	0.87 (0.62-1.15)	0.82 (0.47-1.15)	0.84

Inter-observer variability was calculated using the first round of measurements by both radiologists. The average intra-observer variability was calculated using the average Kappa of both radiologists. Values are Kappa with 95% confidence interval (CI).

Figure 3. CT-scan with bilateral ECAA



CT scan of same patients as figure 2. Showing bilateral ECAA.

DISCUSSION

This explorative study demonstrated that gadolinium enhancement is present in ECAA and that the majority of the included ECAA have gadolinium enhancement, when using a binary scale. Of the cases with bilateral ECAA one patient had gadolinium enhancement in both aneurysms, while the other patient only had gadolinium enhancement in one (Figure 2). The ECAA with enhancement was about 4mm larger in size and had a saccular shape, compared to the contralateral fusiform shaped aneurysm.

Due to the small number of patients no analysis could be done to investigate the association between gadolinium enhancement and baseline aneurysm size or patient specific factors like smoking, hypertension and medication use. Also, because of the small study size we used a binary scale for wall enhancement instead of a degree of enhancement like previous studies have done.[14] Larger studies should determine whether aneurysm specific characteristics like shape and size are correlated to the degree gadolinium enhancement. Gadolium MRA imaging seems like a useful tool to study arterial wall behavior over time in patients with ECAA. Since there is indirect evidence of studies conducted on intracranial aneurysms, reporting on gadolinium enhancement and its association with aneurysm rupture and growth, therefore gadolinium enhancement could also be associated with the size and growth of ECAA.[2,12,] The next step should be to study the degree of arterial wall enhancement using time resolved MR imaging protocols[15], changes in gadolinium uptake over time and the relation with both aneurysm growth and occurrence of cerebrovascular sequalae. Another possible limitation is that aneurysm wall enhancement was done by one observer. However, we choose to do so since previous studies have shown an excellent inter-and intra-observer agreement.[9] So far, we cannot directly relate gadolinium enhancement in relation to underlying etiology. Included aneurysms were most likely caused by either atherosclerotic degeneration or dissection. Although aneurysms caused by dissection did show gadolinium enhancement we cannot rule out if this is part of the dissection process or if it's also caused by ongoing

inflammatory disease. To answer this question, patients with proven carotid dissection should undergo gadolinium scanning in the early phase of dissection and at second stage months later to better understand the recovery process of the arterial wall.

Presence of WML has become a marker of disease severity in patients with carotid artery stenosis and a marker of outcome when comparing different revascularization techniques. This study showed that the Fazekas visual rating scale for WML has a moderate inter-observer agreement and a substantial to excellent intra-observer agreement, this is accordance with the literature.[13,14] A higher agreement was achieved when scoring WML on a binary scale. Also, a previous study has shown a higher agreement when measurements were done repetitively.[13] Regardless of the Fazekas scale, the majority of the patients did have WML in the ipsilateral cerebral hemisphere suggesting that subclinical microembolization could be caused by ECAA. However, all patients had contralateral WML, suggesting that either the WML are caused by systemic disease or that the visual scale is very subjective and susceptive for errors. This finding is also in contrast with the literature, where patients a low prevalence of WML was reported in patients younger then 55 years.[16] A limitation of this study is that the contralateral WML were only scored once by one radiologist.

This is the first study reporting on arterial wall enhancement and the presence of WML in ECAA. With MRI and gadolinium being widely available and safe, it is easy to implement this imaging technique in future studies and in the clinical practice.

CONCLUSION

Gadolinium enhancement and WML are present in asymptomatic ECAAs. Future studies are needed to determine whether the presence of gadolinium enhancement is a predictor of aneurysm instability or growth and whether white matter lesions will remain stable or increase over time. If future studies prove that vessel wall enhancement and an increase in white matter lesions are present in these

asymptomatic ECAAs, then vessel wall MRA may cause a change in the clinical approach and management of asymptomatic ECAAs.

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Chapter 6

Standardization of semiautomatic tortuosity measurements in the carotid artery

Submitted

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ABSTRACT

Objective: Increased arterial tortuosity has been suggested as a predisposing factor for carotid artery dissection, which is an important etiological risk factor for development of extracranial carotid artery aneurysms (ECAA). Prior to comparison with non-ECAA controls, the optimal measurement technique should be defined. This study aimed to determine the difference between software packages in terms of reproducibility and absolute outcome of arterial tortuosity measurements in patients with ECAA.

Methods: Four commercial software packages were compared: 3mensio Vascular (Pie Medical ImagingBV, Maastricht, NL), TeraRecon (Aquarius, Foster City, CA, USA), Vital Images (Toshiba Medical, Minnetonka, MN, USA), and Aycan OsiriX PRO (Aycan MedicalSystems, Rochester, NY, USA). Patients with ECAA were selected from our ECAA registry. Two observers independently scored two rounds of 12 computed tomography angiography (CTA) scans using the packages. The tortuosity index (TI) was calculated from skull base until carotid bifurcation and aortic arch and was defined as the true length of the centerline divided by the straight distance. Intraclass correlation coefficients (ICC) with 95% confidence intervals were calculated to quantify inter- and intra-observer variability within one software package, and differences in measured TI between the packages.

Results: The interobserver agreement was nearly perfect for 3mensio, excellent for Vital Images and OsiriX, and substantial for TeraRecon, with ICC 0.99 (0.96-1.0), 0.90 (0.69-0.97), 0.84 (0.53-0.95), and 0.72 (0.28-0.91), respectively. Intraobserver agreement ranged from ICC 1.0 for 3mensio to 0.91 for TeraRecon. Agreements between software packages on measured TI ranged from ICC 0.99 (0.98 -1.0) for 3mensio vs. OsiriX, to 0.95 (0.82-0.98) for 3mensio vs. 3 TeraRecon. Median time needed to complete one round of measurements was highest for OsiriX (p=0.013).

Conclusion: Carotid artery tortuosity measurements are reproducible and comparable between current commercially available software packages, with high intra-observer agreement. Although the reproducibility differed per software packages, all packages scored an acceptable interobserver agreement. Thus, the type of software package will not influence outcomes of tortuosity measurements.

INTRODUCTION

Increased arterial tortuosity has been suggested as a predisposing factor for carotid artery dissection,[1–3] which is in turn an important etiological risk factor for extracranial carotid artery aneurysm (ECAA) formation.[4] Conversely, although experts in the field have suggested that most ECAA have a relative elongated inflow and outflow track, no validated data exist about arterial tortuosity in ECAA patients. In fact, little is known about the natural clinical course and risk factors for adverse outcome of ECAA patients.[5] If increased arterial tortuosity would exist in ECAA patients, it may aid in individual patient's risk prediction for adverse outcome. In addition, severe tortuosity affects planning and performing interventions for aneurysm exclusion when indicated.[6]

In order to validate the relative tortuosity in patients with ECAA as compared to patients with normal carotid arteries, a comparative study with non-ECAA controls should be set-up.

Beforehand, it is crucial to first establish a standardized method to define and measure the arterial tortuosity. Tortuosity is defined in literature as the property of the artery to have 'many turns'.7 Multiple definitions exist to quantify arterial tortuosity, but due to its good reproducibility values it is commonly referred to as the tortuosity index (TI), which is the true length of the vessel divided by the straight distance.[8–11]

Manual measurements in different arterial territories are reliable, but time consuming.[12–14]

Multiple software packages to facilitate (semiautomatic) TI measurements are commercially available. It is unknown how the tortuosity measurements performed by these different packages relate to each other in terms of inter- and intra-observer variability and differences in absolute[5] measured tortuosity.

Furthermore, it is unknown how increased vascular tortuosity will influence the assessed values within these software packages.
Accordingly, the present study aimed to investigate the difference between these software packages in terms of reproducibility and absolute outcome of carotid artery tortuosity measurements, in patients with an ECAA. [6]

METHODS

Case selection

Datasets of 12 patients with an ECAA all located in the internal carotid artery (ICA) were retrieved from our Carotid Aneurysm Registry (www.carotidaneurysmregistry.com).[15] The registry has been approved by the local ethics committee, and all patients gave informed consent. For the purpose of this study, a computed tomography angiography (CTA) scan with slice thickness below 1.0 millimeter (mm) was eligible for inclusion to guarantee proper slice thickness for reconstruction. This necessary condition limited the amount of eligible CTAs to 12 due to rarity of disease. The CTAs have been performed for evaluation or treatment of ECAA between 2008 and 2017, in the University Medical Center Utrecht. We aimed to select an equal amount of cases with fusiform and saccular ECAA. As specified within the registry protocol, 15 fusiform aneurysms were defined as ≥150% diameter increase of the normal ICA diameter, while saccular aneurysms were defined as a distended sac of any size affecting only part of the ICA circumference.

Imaging

A 64-slice or 128-slice CT scanner (Philips Brilliance; Philips medical systems, Best, the Netherlands) was used to acquire the CTA scans. The carotid arteries were visualized from aortic arch to skull base. Median slice thickness was

0.67mm (range 0.62-0.90mm), increment 0.33, collimation 64x0.625 and pitch 0.609. Radiation exposure parameters were 100-120 kilovolt and 150-300 mill ampere second. The field of view is set per patient. Injection of 65 milliliter intravascular contrast (ultravist 300, Schering, Berlin, Germany) was followed by a saline bolus of 40 milliliter, both at a flow rate of 6 milliliters per second.

Software packages

Our study focused on the evaluation of semiautomatic measurement software packages. A search was performed to identify software packages which facilitated semiautomatic vessel tortuosity measurements and were commercially available. To this end, the MEDLINE database was searched using the search terms 'software', 'length' or 'tortuosity', 'vascular', and synonyms. Availability of free trial licenses was required in order to participate in this comparative study. Four commonly used commercial software packages were selected: 3mensio Vascular (version 8.1, Pie Medical Imaging BV, Maastricht, the Netherlands), Aquarius iNtuition (version 4.4.12.265, iNtuition Cloud, TeraRecon, Foster City, CA, USA), Vitrea (version 7.4, Vital Images Inc., Toshiba Medical, Minnetonka, MN, USA), and Aycan OsiriX PRO (version 3.10.xxx, Aycan Medical Systems, Rochester, NY, USA). All software packages are all commonly used for semiautomatic (vessel) analysis and centerline composition.[16–25]

Study design

Two observers (EEV and VECP) independently scored the 12 datasets at two time points (round 1 and 2, interval ≥1 week) with the four software packages. Observers were blinded to each other's measurements and to earlier measurements with the same software package. For each software package, both observers received a training session by the company of one hour and

practiced three measurements in order to familiarize with the package and overcome the early learning curve.[8]

Outcome measures

In all software programs, carotid artery tortuosity was determined by calculating the tortuosity

index (TI) of the carotid artery ipsilateral to the ECAA. The TI was defined as the true length of

the central luminal line (CLL) divided by the straight distance. It was calculated in two ways:

from the skull base (just proximal from the carotid siphon) until 1) carotid bifurcation and 2) aortic arch (Figure 1). The primary outcome measure was the reproducibility of tortuosity measurements, expressed as the inter- and intra-observer variability in the TI, as measured with the different software programs. The secondary outcome measure was defined as the agreement in absolute TI between the software programs. For both the primary and secondary outcome measures, the correlation between measurements was calculated by using the TI from skull base to carotid bifurcation, since ECAAs are located primarily in the ICA. The tertiary outcome measure was the time needed per scan (difference in time between scoring round 1 and 2 (learning curve).

STATISTICS

Inter- and intra-observer variability

The intraclass correlation coefficient (ICC) was used to calculate the inter- and intra-observer variability for measurements obtained with one software package (model: two-way mixed, type: consistency). An ICC of 1.0 equals perfect agreement, an ICC of 0.81-0.99 excellent agreement, and an ICC of

0.61-0.80 substantial agreement.26 The first round of measurements of both investigators was compared in order to calculate interobserver variability for each software[9] package. Bland-Altman plots were constructed to assess presence of systematic differences between both observers.

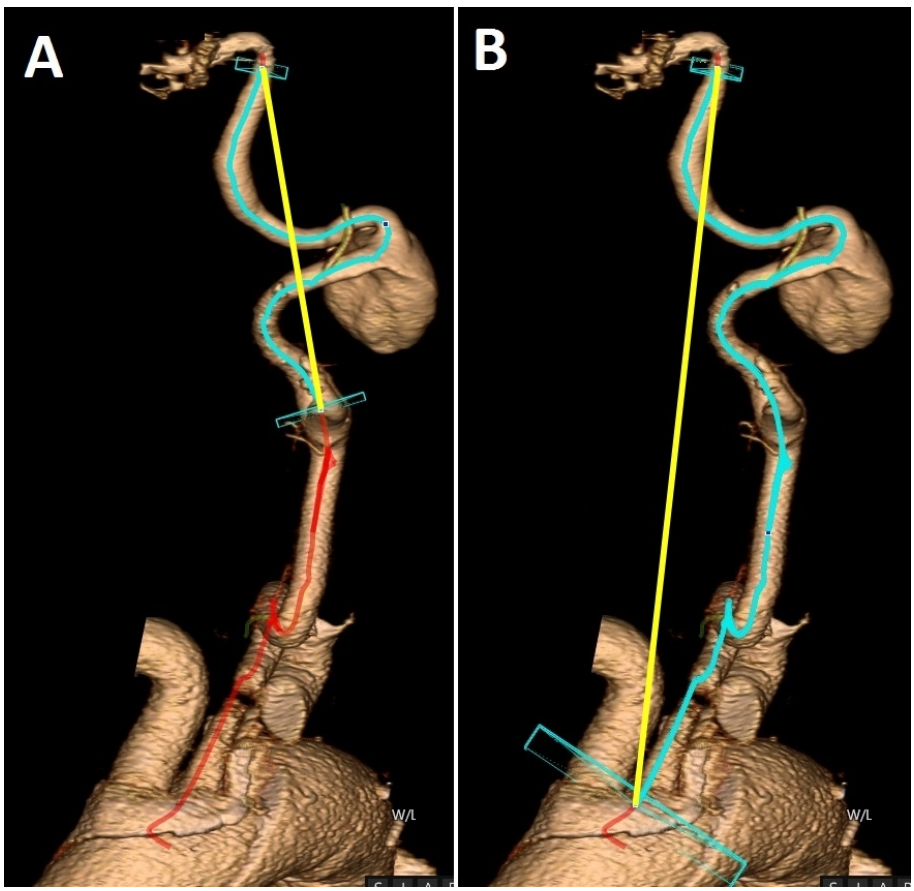

Figure 1. In each dataset, carotid artery tortuosity index (TI) was calculated from skull base until (A) carotid bifurcation, and (B) aortic arch (this rendering using Vital Images software). A left internal carotid artery (ICA) with a saccular ECAA is shown, depicted from aortic arch until the cavernous part of the ICA. The blue line indicates the part of the centerline (in red) that was used to measure the TI of the ICA (A) or ICA plus common carotid artery (B). This true length was divided by the straight distance (shown in yellow).

Agreement on absolute TI

The ICC was also used to calculate agreements on obtained TIs per software package. In order to

calculate the differences in measured absolute TI with each software package, the average TI (TIaverage) per case was calculated by taking the average of all four measurements. This was done for each software package separately, thereby producing one TIaverage per software package for each of the 12 cases.

Time needed per scan and learning curve

A Kruskal-Wallis test was used to calculate differences between software packages in time needed to complete all measurements, while a Wilcoxon signed rank test was used to calculate differences in time needed to complete round 1 and 2 within one software package. Mann-Whitney U tests were used as post-hoc tests, and Bonferroni correction was applied to account for multiple testing. Statistical analyses were conducted using SPSS 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). A P-value less than 0.05 was considered statistically significant.[10]

RESULTS

Patient and aneurysm characteristics

Most ECAA patients were male (n=7; 58%) with a median age of 62 years (range 25-80 years). Aneurysms were saccular (n=7; 58%), or fusiform (n=5; 42%). The median aneurysm diameter reported in the patient records was 12 mm (range 7-40 mm) for saccular aneurysms, and 11 mm (range 5-32 mm) for fusiform aneurysms (Table 1).

Table 1. Patient and aneurysm characteristics.

Characteristic	ECAA (n=12)
Male	7 (58)
Age (years)	62 (25-80)
Left carotid artery affected	6 (50)
Aneurysm shape	
- saccular	7 (58)
- fusiform	5 (42)
Reported aneurysm diameter (mm)	
- saccular	12 (7-40)
- fusiform	11 (5-32)

NB. Data are given as numbers (percentage) or median (range).
Abbreviations: ECAA= extracranial carotid artery aneurysm.

Reproducibility of measurements

Inter- and intraclass correlations between software packages are summarized in Table 2. The agreement between both observers was nearly perfect for measurements performed with 3mensio, excellent for Vital Images and OsiriX, and substantial for TeraRecon. Bland and Altman plots were visually evaluated and revealed no clear systematic differences between both observers (Figure 2). The average intra-observer variability ranged from a perfect agreement of 1.0 for 3mensio to 0.91 for TeraRecon.

Table 2. Inter- and intra-observer variability of tortuosity index (TI), measured from carotid bifurcation to skull base.

	Inter-observer variability	Intra-observer variability (observer 1)	Intra-observer variability (observer 2)	Average intra-observer variability
3mensio	0.99 (0.96-1.0)	1.0 (0.99-1.0)	0.99 (0.96-1.0)	1.0
TeraRecon	0.72 (0.28-0.91)	0.97 (0.90-0.99)	0.85 (0.55-0.95) *	0.91
Vital Images	0.90 (0.69-0.97)	0.99 (0.97-1.0)	0.97 (0.86-0.99)	0.98
OsiriX	0.84 (0.53-0.95)	0.95 (0.85-0.99)	0.90 (0.68-0.97)	0.93

NB. Interobserver variability was calculated using the first round of measurement of both observers. The average intra-observer variability was calculated as the average ICC of observer 1 and 2.
Values are intraclass correlation coefficient (ICC) with 95% confidence interval (CI).
Footnotes: *ICC based on 9 out of 12 cases.

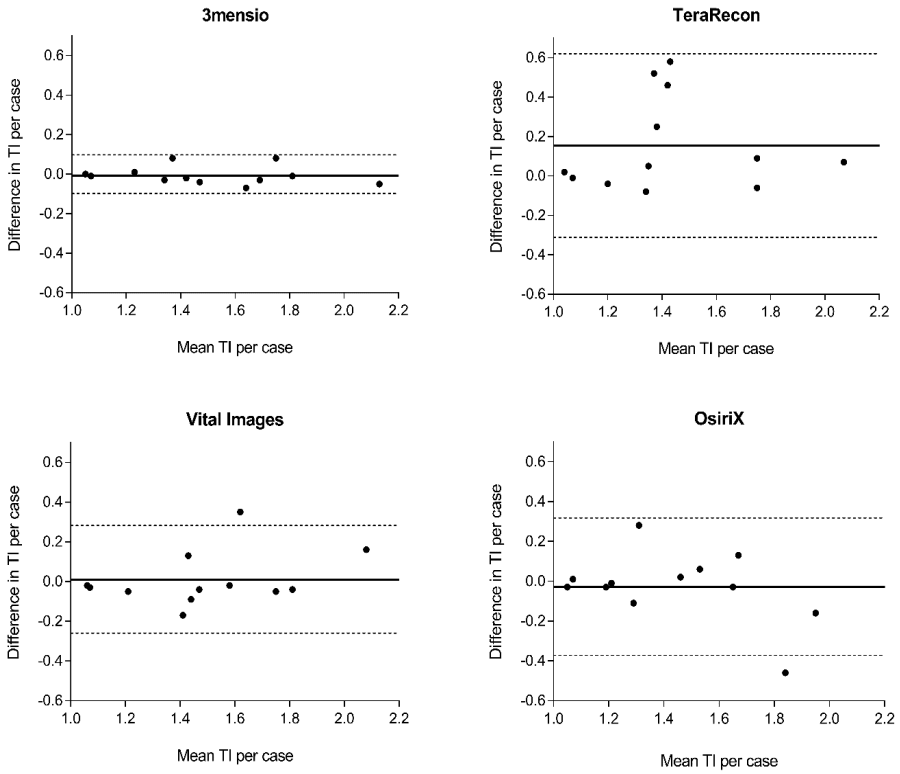

Figure 2. Bland-Altman plots showing agreement of two observers on measured TI for each of the 12 cases. Each graph represents a different software package. The line in the middle represents the mean difference of the TI between the two observers, and the two dotted lines represent the upper and lower limits of agreement (mean difference ± 1.96 * standard deviation).

Comparison of measured tortuosity indices

In order to calculate the differences in absolute measured TIaverage with each software package, the ICC was calculated for each software comparison (Table 3). Agreement on measured average TIs between all four packages was excellent, as the ICC for these comparisons equaled 0.95 or higher. Thus, all software packages measured similar TIs for the 12 cases. The median TIaverage of the 12 cases was 1.42 (interquartile range [IQR] 1.29-1.65) from

carotid bifurcation until skull base, versus 1.29 (IQR 1.15-1.45) from aortic arch until skull base. [11] Of note, in OsiriX software the straight distance had to be drawn in one and the same sagittal/coronal slice even if the skull base and proximal endpoint (bifurcation or aortic arch) was located in a different slice, which could have led to an overestimation of the TI.

Table 3. Intraclass correlation coefficients (ICCs) with 95% confidence intervals (CIs) of for each software package comparison of the average tortuosity indices ($TI_{average}$).

Software comparison	ICC (95% CI)
3mensio vs TeraRecon	0.95 (0.82-0.98)
3mensio vs Vital Images	0.98 (0.91-1.0)
3mensio vs OsiriX	0.99 (0.98-1.0)
TeraRecon vs Vital Images	0.99 (0.96-1.0)
TeraRecon vs OsiriX	0.95 (0.83-0.99)
Vital Images vs OsiriX	0.99 (0.96-1.0)

Usability of the software packages

The time needed to complete the first round of measurements was comparable between 3mensio, TeraRecon and Vital Images, with time ranging from a median of 8.5 (IQR 5.0-14.8) minutes for TeraRecon to 11.8 (IQR 5.8-15.6) minutes for Vital Images, while OsiriX software took median 16.8 (IQR 14.4-18.5) minutes (Figure 3). This difference was significant for both round 1 ($p=0.013$) and round 2 ($p<0.001$), and post-hoc tests revealed that OsiriX took significantly longer than the other software packages. Since the number of corrections needed to create a proper fit for the CLL was graded equal for all

packages, this difference was probably attributable to a longer time-to-segmentation of the carotid artery for OsiriX software. Except for TeraRecon, round 2 of measurements took significantly shorter compared to round 1. Thus, the usage of the software packages seemed to encompass a significant learning curve (but without influencing reproducibility).[12]

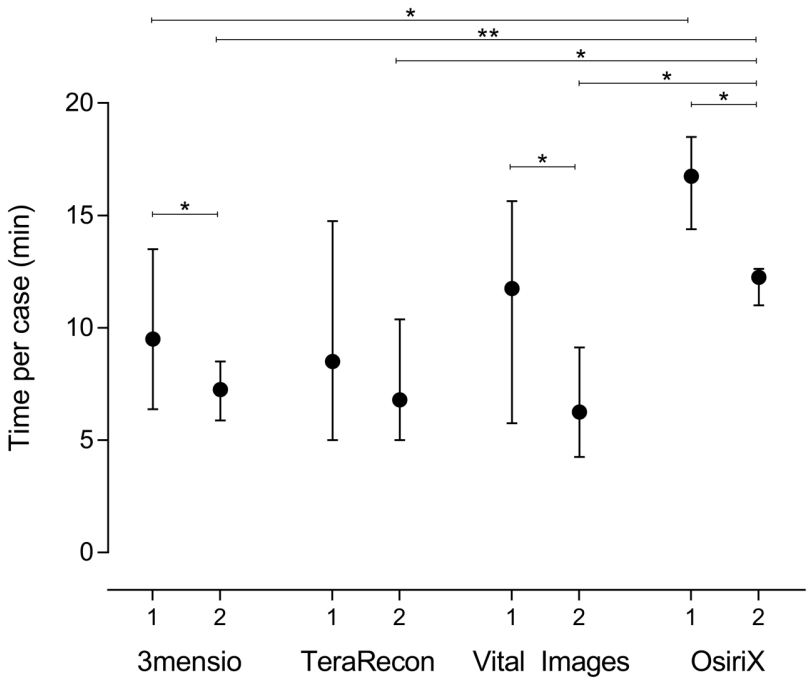

Figure 3. Time needed to complete the first and second round of measurements, for each software package separately. Significant differences are flagged with: * $p<0.008$, ** $p<0.001$. Due to Bonferroni correction for multiple testing, the significance level was set at $p<0.008$ for comparisons between software packages (Mann-Whitney U test), and at $p<0.013$ for comparisons between round 1 and 2 within a software package (Wilcoxon signed rank test).

DISCUSSION

The present study shows that carotid artery tortuosity measurements are reproducible and comparable between the four commercially available software packages that were included in this analysis: 3mensio, TeraRecon, Vital Images and OsiriX. Calculated interobserver agreements ranged from 0.99 to 0.72, and agreements between the packages on measured absolute tortuosity indices equaled 0.95 or higher. This suggests that all four software packages can be applied for TI measurements of carotid arteries, and that obtained results with these different software packages are comparable. A range of different software packages is being used for assessment of vessel anatomies. As clinicians often have limited access to direct comparisons to aid in software selection, it is unclear whether outcomes of these software packages are comparable. To our knowledge, few research groups examined comparability of software packages for measurements on patient vessels. Three papers focused on (phantom) abdominal aneurysm diameter measurements, and demonstrated high levels of agreement for 3mensio, TeraRecon and Simbionix PRORS software (ICC $\geq$ 0.82),16,17 or TeraRecon versus OsiriX software (ICC $\geq$ 0.82).24 A comparison of 3mensio, TeraRecon, Philips and Siemens software demonstrated good correlations for semiautomatic carotid stenosis measurements with manual measurements (ICC $\geq$ 0.81).[19] However, high vessel tortuosity is likely to challenge semiautomatic centerline composition. We found a median tortuosity index of 1.42 for the internal carotid artery of these ECAA patients, which is deemed higher than the 1.19 of normal internal carotid arteries.[18] Obviously, these data need to be evaluated in more detail in a direct comparison with non-ECAA controls. Nevertheless, the present study shows that even in these challenging vessels, tortuosity measurements remain comparable between software packages. Although fully automated [13] measurements would most likely increase observer agreement

and lower time consumption, we believe manual correction of the centerlines will often be required to ensure accuracy of measurements, especially in these tortuous cases. Currently, little is known about the natural clinical course of patients with an ECAA,[5,27] and no guidelines exist regarding treatment or follow-up. Increased tortuosity values have been linked to increased clinical risk of dissection in different arterial territories.[11,28] However, whether these vessels were tortuous at baseline and therefore a cause of ECAA formation or merely a consequence, remains to be elucidated. Nonetheless, carotid artery tortuosity in ECAA patients has potential as a risk predictor of adverse outcome and may provide valuable additional sensitivity for the individual ECAA patient's risk prediction. There are several limitations to the present study. Due to rarity of disease, only 12 cases could be included in this pilot study. Moreover, merely two observers scored the scans, both with over one year of experience with these specific carotid CTA scans. As the primary purpose of this study

was to compare the performance of the software programs rather than assessing the true TI values, we consider a good interobserver reliability between these similarly trained observers most relevant and sufficient. Also, both observers scored the software packages in a different order, but the 12 cases were measured in a non-randomized fashion; therefore, a learning curve might have influenced results obtained for the first and last cases. However, as all packages scored high inter- and intra-observer agreements this effect may be considered negligible. Finally, it is unknown how little changes in head posture during scanning might influence carotid arteries tortuosity indices. If found relevant, future studies should consider scanning the patients with their head in locked position to rule out confounding due to different head postures.[14]

CONCLUSIONS

In summary, semiautomated carotid artery tortuosity measurements are reproducible and comparable between software packages. Although the reproducibility differed per software packages, all packages scored an acceptable interobserver agreement. This suggests that the type of software package will not influence outcomes of tortuosity measurements in highly tortuous carotid arteries, and that all four software packages are valid for measuring TI.

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Chapter 7

Experience of a single center in the conservative approach of 20 consecutive cases of asymptomatic extracranial carotid artery aneurysms.

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ABSTRACT

Background: The clinical course and optimal treatment strategy for asymptomatic aneurysms of the extracranial carotid artery (ECAA) are unknown. We report our single-center experience with conservative management of patients with an asymptomatic ECAA.

Methods: A search in our hospital records from 1998 to 2013 revealed 20 patients (mean age 52 years, SD 12.5) with 23 ECAA, defined as a 150% or more fusiform dilation or any saccular dilatation compared to the healthy internal carotid artery. None of the aneurysms was treated; we had no predefined follow-up schedule for these patients. The primary study endpoint was the yearly rate for ipsilateral ischemic stroke. Secondary endpoints were ipsilateral transient ischemic attack, any stroke related death, other symptoms related to the aneurysm or growth defined as any diameter increase.

Results: ECAA were either fusiform (n = 6; mean diameter 10.2 mm) or saccular (n=17; mean diameter 10.9 mm). Eleven (55%) patients with 13 ECAA received antithrombotic medication. During follow up (median 46.5 months; range 1 - 121 months), one patient died due to ipsilateral stroke; ipsilateral cerebral stroke rate was 1.1 per 100 patient years (95% CI 0.01 – 6.3). Three patients had ECAA growth; two were asymptomatic, one was the patient who stroked.

Conclusion: In this retrospective case series, patients with an asymptomatic ECAA the risk for cerebral infarction is small but not negligible. Conservative management seems justified, in particular in patients without growth. Large prospective registry data are necessary to assess follow up imaging strategies and the role of antiplatelet therapy.

INTRODUCTION

Aneurysms of the extracranial carotid artery (ECAA) are rare. Just over 1000 cases with ECAA have been reported in world literature thus far.[1] The etiology is diverse and ranges from atherosclerosis, infection, granulomatous disease, to (traumatic) dissection [2]. Most ECAA are asymptomatic and are coincidental findings during imaging for alternative pathologies. However, ECAA may progress into a pulsatile mass, cranial nerve compression or cause a stroke.[3-5]
Little is known about the natural history. Previous studies that included aneurysms with different causes, have reported the natural course of ECAA with a combined stroke and mortality rate of over 50%, suggesting a low threshold for invasive treatment.[6-8] A recent systematic review reported lack of growth during follow-up or even shrinkage of post carotid artery dissection aneurysms, suggesting that a that a conservative approach is justified for these aneurysms.[9] However, the studies included in this review consisted of symptomatic and asymptomatic patients, with no data on aneurysm size or growth, nor on the interval of imaging follow-up.[9] With the lack of data on the natural course of asymptomatic ECAA, we aimed to assessed in a single center series the outcome of patients with asymptomatic ECAA receiving conservative treatment and follow-up.

METHODS

Patients

Based on hospital record search we analyzed a series of 20 patients, either referred for, or with ECAA as a coincidental imaging finding in our tertiary vascular referral and stroke center within the University Medical Center Utrecht (UMCU), The Netherlands between January 1998 and December

2013. Patients with at least one follow-up visit at the outpatient clinic were included. Data on patient characteristics, aneurysm characteristics, intervention, and short and long-term outcomes were collected from patient records using a pre-specified form. Patients were considered asymptomatic if they experienced no neurological events in the recent six months prior to presentation. In patients with bilateral ECAA of which one side was previously symptomatic, only the asymptomatic side was included for analysis. The study was approved by the medical ethical committee of the UMCU.

ECAA

An ECAA was defined as a 150% or more fusiform dilatation of the normal vessel diameter or (saccular) distended sac of any size. For the present analysis, the ECAA had to be in the internal carotid artery between the carotid bifurcation and the carotid siphon at the skull base.

Outcome

Follow-up was performed on a personalized basis, without a pre-defined scheme. The primary outcome was ipsilateral ischemic stroke. Secondary outcomes were ipsilateral transient ischemic attack (TIA), any stroke related death (including major bleeding), growth or any possible aneurysm related symptoms other than stroke, observed during follow-up. Symptoms considered to be aneurysm related were local cervical pain or sensory sensations (due to a palpable mass in the neck), ipsilateral cranial nerve dysfunction (including hoarseness and dysphagia), or aneurysm rupture. Growth was defined as any diameter increase and was determined by comparing the measured diameters in the radiology reports.

Statistical analysis

For continuous variables, means, median and standard deviations (SD) or medians and ranges were calculated, and for categorical variables, absolute numbers and/or percentages were calculated. We calculated the stroke rate, the rate for the secondary outcomes and corresponding 95% confidence intervals (CIs).

RESULTS

Patients

We included 20 patients; their characteristics and risk factors are presented in Table 1. Eight patients had bilateral ECAAs, of whom five were symptomatic; thus, a total of 23 asymptomatic ECAAs remained. The diagnosis was established on imaging by computed tomography angiography (CTA) in eight patients, magnetic resonance imaging (MRA's) in six, or digital subtraction angiography (DSA) in one. The median follow-up of patients was 46.5 months (range 1-121 months), with in total 53 CTA's, 10 magnetic resonance angiography (MRA's), 20 duplex ultrasound and three DSA in two patients (one DSA due to a TIA at a contralateral (ECAA) side and one after coiling of a caroticovenous fistula, also on the contralateral side). Patient treatment and follow up regimen was determined by the treating physician after multi-disciplinary conference and was based on symptoms, growth and the size of the ECAA.

ECAA characteristics

17 aneurysms were saccular and 16 were localized in the distal ICA (Table 2). The mean diameter of the saccular aneurysms was 10.9 mm (range 4-31 mm) and of the fusiform aneurysms 10.2 mm (range 8-13.4 mm). Five out of the 23

included ECAAs were discovered in patients during follow-up after initial presentation with a symptomatic ECAA on the contralateral side (n= 3 after dissection). Three of these contralateral symptomatic ECAAs were treated surgically, one received APT and the other did not receive any medical or surgical treatment. The other ECAA's were discovered during neurological follow up after contralateral hemorrhagic or ischemic stroke, screening for suspicion for TIA, follow up of connective tissue disease or as a coincidental finding.

Table 1. Patient characteristics, risk factors and clinical presentation

	n=20	Percentage (%)
Male	14	70
Mean age	52.2	
Hypertension	12	60
COPD	0	0
Hyperlipidemia	6	30
Smoking		
Current smoker	4	20
Previous smoker	6	30
DM	1	5
Coronary heart disease	3	15
Peripheral arterial disease	1	5
Non-cerebrovascular aneurysms	3	15
Clinical presentation		
Coincidental finding	8	40
Neurological symptoms	10	50
Follow up Connective tissue disease	2	10

N= number of patients; DM= diabetes mellitus

Table 2. Aneurysm characteristics

	n =23	Percentage (%)
Side		
Left	10	43.5
Location		
Distal ICA	16	69.6
Proximal ICA	7	30.4
Shape		
Saccular Fusiform	17 6	74 26
Size (mean mm, range)		26
Saccular	10.9 (4-31)	
Fusiform	10.2 (8-13.4)	
N= number of aneurysms; ICA= internal carotid artery		

Outcome

During follow-up one patient with an initial 20 mm saccular aneurysm of the left ICA and no antiplatelet or anticoagulant medication was advised to undergo surgical resection because of identified growth to a diameter of 24 mm in eight months but she declined. This patient was admitted to hospital because of a stroke in the posterior circulation 13 months after the initial ECAA diagnosis. During admission, this patient had an additional major stroke in the cerebral territory of the ipsilateral middle cerebral artery, which was eventually fatal. The electrocardiogram showed atrial fibrillation and a CTA showed thrombosis of the entire middle cerebral artery (MCA) and ICA distal of the aneurysm. The calculated ipsilateral cerebral stroke rate was 1.1 per 100 patient years (95% CI 0.014 – 6.28).

Two other patients had an asymptomatic aneurysm growth resulting in a growth rate of 3.4 per 100 patient years (95% CI 0.9-9.2). One patient with a

(initial 12 mm and during follow-up after 59 months 16mm) saccular aneurysm of the right distal ICA, underwent a combined surgical and endovascular procedure with a bare metal stent. The patient was asymptomatic during the entire 75-month follow-up period after surgery. The third patient with a fusiform ECAA with growth of the right distal ICA (initially 8 mm and during follow up 9 mm over 57 months' time) remained asymptomatic with conservative treatment. Two patients died during follow-up from causes unrelated to an ECAA and all other patients remained asymptomatic during follow up.

Figure 1. Progression of extracranial carotid artery aneurysms over time.

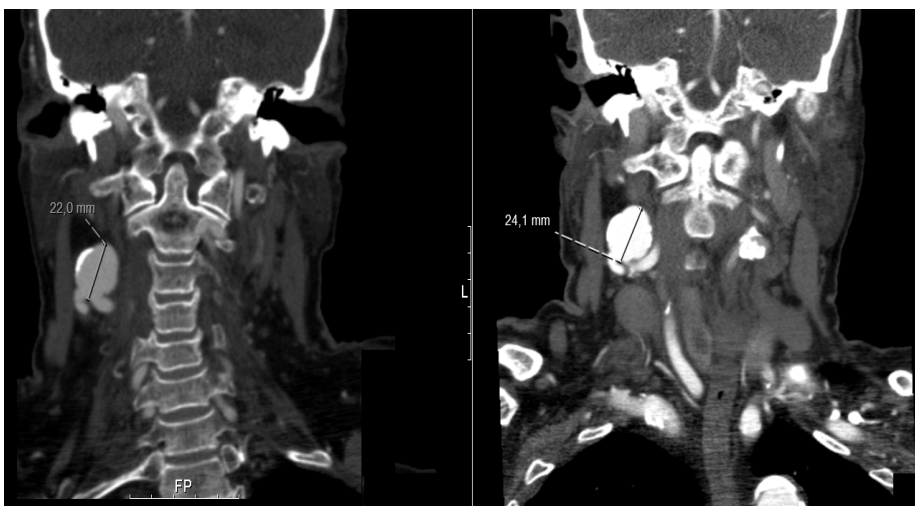
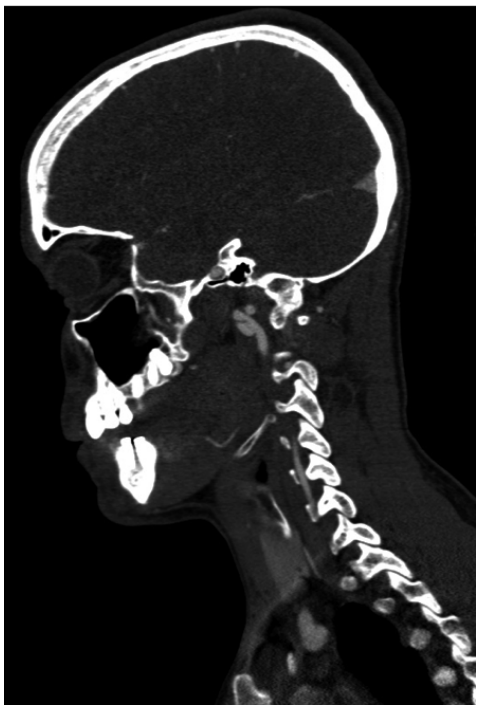


Figure 2. Saccular aneurysm



DISCUSSION

This case series of 20 consecutive patients with 23 ECAA shows that one patient had a fatal cerebral infarction in the territory of the affected carotid artery during follow-up while initially having an asymptomatic ECAA. This patient also had atrial fibrillation indicating another possible cause of the stroke. Two other patients also had growth of their asymptomatic ECAA, while only one was treated endovascularly.

This current study, as far as we know, is the largest study reporting experiences of conservative management of specifically asymptomatic ECAA.[1] Another study reporting ten cases of asymptomatic ECAA treated conservatively reported a benign clinical course of asymptomatic dissection aneurysm. [10]

The low stroke and mortality rate we found for conservative management of ECAA is also in agreement with another publication on conservative management in ECAA, which described a series of patients with dissecting aneurysms.[9] The majority of the dissecting aneurysms remained asymptomatic and did not increase in size while some even spontaneously resolved.[9] Another study also reports a low aneurysm related death in non-operatively treated group, however all the studies we found included symptomatic and asymptomatic patients.[9-11]

The previously suggested high stroke and mortality rate is mainly derived from literature dating back to one to more than three decades ago.[6,7] On the basis of this suggested high mortality and morbidity rate, many aneurysms of the extracranial carotid artery have been treated invasively. It must be noted that this rate included aneurysms of all etiology, and included mycotic, symptomatic and growing aneurysms. Furthermore, these patients were not treated with anticoagulant or antiplatelet medication, which is currently a well-accepted preventive therapy for cardiovascular events, although not proven to be effective in ECAA patients.[12]

It must be noted that the stroke rate might even be less than the one we found, since the stroke observed in our study was most likely caused by cardiac embolism due to atrial fibrillation.

This study has limitations, first of all, because the retrospective character there was no standardized follow-up schedule and may have led to missing data regarding aneurysm and patient characteristics. Also, in some cases the physician ceased the follow-up for unknown reasons. Secondly, there is selection bias, the sample in this study consists of patients in whom the treating physician selected a treatment strategy based on the patient's clinical presentation and aneurysm characteristics. This is due to a lack of guidelines for medical treatment. Finally, this study contains a group of patients with different etiology. Despite, this case series offers a large series with a relatively

long term follow up and provides additional insights in the prognosis of ECAA in asymptomatic patients. A larger prospective registry-based patient population further analyzing the natural course of ECAA in asymptomatic patients is clearly needed to substantiate treatment guidelines.[13] Also, medical therapy for ECAA that has so far been unexplored, needs to be investigated further.

CONCLUSION

In conclusion, this retrospective single center study showed that patients with an asymptomatic ECAA have a rate of ischemic stroke in the aneurysm territory of 1.1 per 100 patient years. Most aneurysms do not grow over time and remain asymptomatic. Large data reporting long-term natural follow-up are warranted.

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Chapter 8

Treatment of extracranial carotid aneurysm: a review of the literature

Submitted

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ABSTRACT

Purpose: To analyze the available literature on the evidence and trends on treatment of asymptomatic or symptomatic Extracranial Carotid Artery Aneurysms (ECAAs).

Methods: All studies on ECAA treatment including case reports were searched until May 2017. All studies reporting on the conservative or invasive treatment of ECAA, on both asymptomatic and symptomatic patients, were included.

Results: A total of 256 studies including 211 case reports were selected on a total of 1816 patients with 1921 ECAAs. The most reported etiology of ECAA was atherosclerosis (30%). Of the ECAAs, 1507 (78%) were symptomatic, with a local pulsating mass as the most reported symptom (30%). Open surgical procedures (74%) were the most reported treatment. More recent evidence on endovascular ECAA exclusion was limited to 15 case reports and 4. small case series.

Conclusions: The majority of the published data on ECAA report the surgical treatment and short-term outcome of symptomatic ECAA. Insight in endovascular therapies, long term outcome, and the natural history is essential to learn about the risk/benefit ratio of ECAA exclusion.

INTRODUCTION

Extracranial carotid aneurysms (ECAA) are infrequently diagnosed and because of its rarity little is known about the specific pathology and the best therapeutic strategy.[1,2] Treatment of ECAA is aims to reduce the risk of future neurological sequalae. The treatment choices, either conservative or invasive, depend on the clinical presentation of the ECAA, the presumed etiology, the condition of the patient and the location of the ECAA.[3] Surgical ECAA exclusion has been considered the treatment of choice for symptomatic or growing ECAA.[3] More recently, based on a small single center series with midterm follow-up, a conservative approach has been suggested to be acceptable in asymptomatic patients with non-growing ECAA.[4]

Best medical treatment may hold antithrombotic treatment and regular follow-up, but no treatment algorithm exists, and guidelines are lacking. Invasive treatment includes both open surgery or endovascular techniques. Traditional surgical treatment of ECAA consists of open resection of the complete aneurysm with or without replacement with an interposition graft including stent placements.[5,6] For a proper assessment what treatment is preferable in which patient, a better understanding on the benefit of medical or invasive treatment in both asymptomatic and symptomatic patients is required. We performed a systematic review of all the available published literature regarding the outcome of treatment and the treatment trends in patients with ECAA.

METHODS

Literature search

On May 31th 2017 a systematic search was performed for all literature since 1900 in Pubmed and Embase using the following search terms: 'Aneurysm', 'carotid (artery)', 'treatment', 'management', 'extracranial', and synonyms for treatment options. Moreover, the term 'intracranial' was used to exclude articles in the literature search. The present search was an update of the 2014 Welleweerd et all.[7] series while in our present analysis we allowed all studies including case reports.

Selection of studies

Studies were selected based on title, abstract, and a full-text screening by two authors (T.M., V.P.). Articles describing aneurysms located in the extracranial part of the internal carotid artery (ICA), external carotid artery (ECA), and/or the common carotid artery (CCA) were included. Also, articles reporting on ECAA and its treatment were included. Studies were excluded if they described aneurysms located intracranially, had inconclusive data, the full text was unavailable, or when the written language was not English.

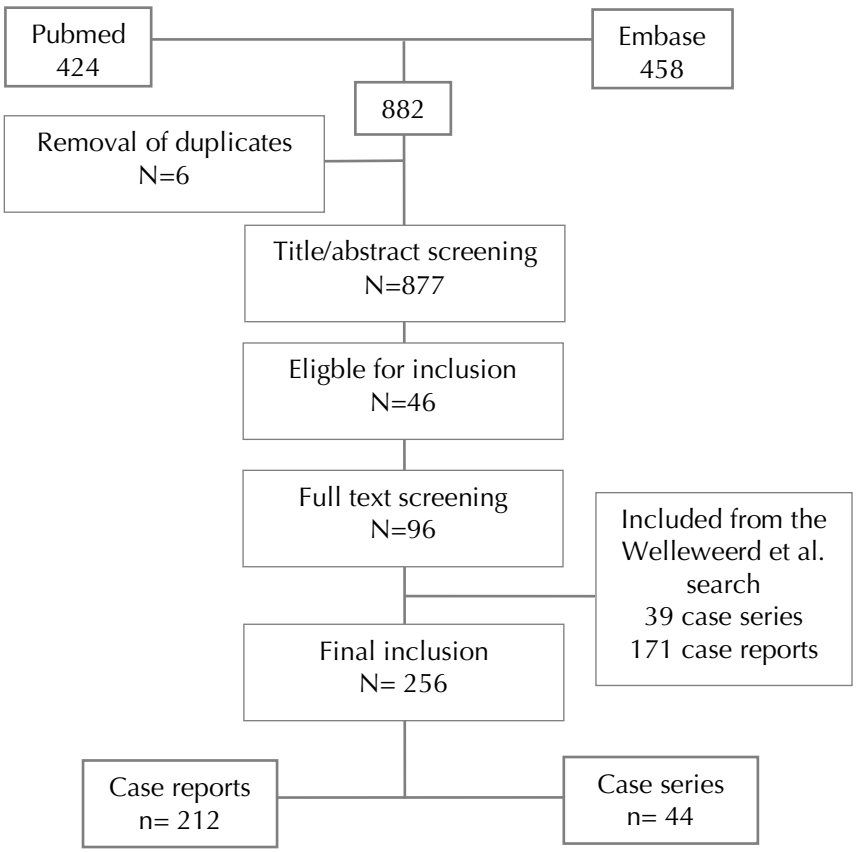
The following data was retrieved from the included articles: number of patients, number of aneurysms, patient characteristics, presumed etiology, symptoms, aneurysm characteristics, type of intervention, follow-up, and outcome. Patient characteristics include sex, age, smoking, diabetes, medical history (cardiovascular and neurological), family history, hyperlipidemia, and hypertension. Aneurysms characteristics collected were affected side, location, shape and size.

RESULTS

Articles

After removing duplicates, our search identified a total of 877 articles. After screening on title, abstract, and full text, 46 new articles were found. Thereafter we screened the studies found in the 2014 search by Welleweerd et al. After including these articles, a total 256 articles were eligible for inclusion of which 211 case reports (Figure 1). A complete list of the included articles can be found in the APPENDIX[1-256].

Figure 1. Flow chart of the article selection



Patient and aneurysm characteristics

Our search retrieved a total of 1816 patients with 1921 aneurysms. Of all the included aneurysms (78%) were symptomatic. There were 17 case series describing 172 asymptomatic ECAAs and 37 case reports. In 15 case reports and one case series (n=200 ECAA, 10%) it was unclear whether patients were symptomatic. The most reported symptom was a local pulsating mass (n=564, 30%). Other reported symptoms were TIA (18%), stroke (12%) and local compression (11%). Three case reports reported a rupture in 4 patients, of whom two had a mycotic aneurysm and the other two a rupture of a post-surgical/iatrogenic pseudo-aneurysm.

Atherosclerosis was the most reported cause of ECAA (n=556, 29%) along with dissection and trauma (13%). The patient and aneurysm characteristics are presented in Table 1.

Table 1. Aneurysm characteristics

Variables	N	Percentage (%)
Articles included	255	
Patients	1816	
ECAA	1921	
Etiology		**n=1921**
Atherosclerosis	559	29
Dissection	251	13
Trauma	242	13
Other	497	26
Not reported	372	19
Symptoms		**n=1921**
Pulsating mass	569	30
TIA	352	18
Stroke	238	12
Local compression	208	11
Other	140	7
Asymptomatic	214	11
Not reported	200	10

Table 1. ***Continued***

Location		
ICA	874	45
Bifurcation	307	16
CCA	183	10
ECA	14	1
NR	540	28

[a]Includes: mycotic, iatrogenic, connective tissue disease, fibromuscular disease, vasculitis. [b] Includes: hoarseness, horner syndrome, dysphagia and pain. [c] includes: rupture, hematoma. Abbreviations: N = number, ECAA= extracranial carotid artery aneurysms, TIA= transient ischemic attack, ICA= internal carotid artery, CCA= common carotid artery, ECA= externa carotid artery, NR = not reported.

Treatment

The majority of the ECAA (90%) were treated invasively (Table 2): surgery (68%), endovascular treatments or a combination of both (Hybrid). A conservative approach was performed in 10% of the reported cases. When comparing the treatments of before and after 2014 is becomes apparent that more endovascular treatments have been reported in the recent literature (80%) in comparison with the literature before 2014 (10%).

TABLE 2. Treatment of ECAA. N=1921

Intervention	N	Percentage (%)
Surgery	1307	74
Endovascular	256	15
Hybrid	24	1
Conservative	334	10

Conservative included medication. Abbreviations: N = number, ECAA= extracranial carotid artery aneurysms.

Outcome

The follow up duration of the case series was most often presented as a mean of the population; therefore, it was impossible to determine the exact follow up duration. In total 100 (6%) patients were reported to have died during follow up, of which 19 due a fatal stroke. The rest of the patients (n=81) died to causes unrelated to ECAA. The surgery group had the highest mortality rate then the other treatment groups (Table 3). It was also only group with local nerve damage post-operatively.

Of the patients treated conservatively, only six case reports described an uneventful course after 1-96 months. One patient with an untreated mycotic aneurysm died 2 days after hospital admission. Most of the studies describing a surgical or conservative treatment did not report the outcome.

TABLE 3. Treatment outcome of ECAA

Intervention	Non-fatal stroke	Fatal stroke	TIA	CND	Death unrelated to ECAA	Re-intervention	NR
Surgery	3%	5%	0.2%	8.8%	5.6%	0.2%	81%
Endovascular	0.4%	0.4%	0	0	1.2%	9%	26%
Conservative	0	1.2%	0	0	1.2&	6.8%	85%

Abbreviations: ECAA= extracranial carotid artery aneurysms. TIA= transient ischemic attack, CND = cranial nerve deficit. NR= not reported

DISCUSSION

Because of the rarity of ECAA little is known about the best treatment approach. A previous literature review focused on the results of treatment as reported in larger case series.[7] However, due to the scarcity of the disease most reports consist of case descriptions or small case series. Therefore, in the present analysis, we included all the available literature reporting on the treatment of ECAA until now.

Although it is anticipated that a substantial portion of ECAA may remain clinically silent and even show regression of the ECAA, ECAA may lead to neurologic symptoms when left untreated. The most commonly reported etiology in our study was atherosclerosis, which is in accordance with previous publications.[8] Local pain, a (pulsatile) mass, and/or local compression are known to be characteristic for ECAAs and are seen in the majority of the included patients.

In this systematic review comprising all available published data reported on ECAA, we found that most patients in the literature were treated for symptomatic ECAA. This finding is most likely caused by publication bias.

One in every six patients included in this study was treated for asymptomatic ECAA, some of whom have been treated invasively. It would have been interesting to compare the treatment outcomes in this select subgroup. However, because the data was presented at group level mostly in case series with heterogenous study populations this analysis was impossible. The benefit of ECAA exclusion in asymptomatic patients therefore is still unknown, and it remains unclear whether asymptomatic patients should be exposed to the risks invasive treatments. Furthermore, with only a limited 334 reported patients having conservative treatment, there is no reliable data on the natural course of ECAA.

Currently, no guideline is available regarding the optimal management strategy for ECAAs. There is a variety of treatment options for symptomatic patients and an invasive approach is often the method of choice. Long-term results must reveal which treatment option is favorable for an advantageous outcome. Efforts to prospectively follow-up all patients with an ECAA are already being done and are relevant to learn more about the natural history of this rare disease.[9] This web-based registry has been designed to collect data on patients with ECAA and to guide management in the future.

Although, this is the largest study providing all the available data on the treatment of ECAA, its does have its limitations. There are no randomized control trails reporting in the treatment of ECAA and our assessment is limited to the data provided by the articles included. This results in a lot of missing information. The outcome after the surgical and conservative approach of most the patients is missing. Therefore, we cannot adequately asses the short and long-term outcome. Also, the included studies reported ECAA caused by different etiologies, therefore making it difficult to imply to any ECAA. The

natural history of ECAAs is still unclear and management is mainly based on articles of more than a decade old reporting on mainly invasive treatments. Another limitation is that there are a lot of case reports included in this search, which also causes publication bias. Generally, researchers tend to publish only successful cases. Due to this publication bias and heterogeneity of the ECAA etiology, the results may not be applicable to the whole ECAA population.

CONCLUSIONS

The majority of the published data on ECAA report the surgical treatment and short-term outcome of symptomatic ECAA. Insight in endovascular therapies, long term outcome, and the natural history is essential to learn about the risk/benefit ratio of ECAA exclusion.

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Chapter 9

Which carotid artery aneurysms need to be treated (and how)?

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ABSTRACT

Extra-cranial carotid artery aneurysms (ECAA) are uncommon and represent a therapeutic challenge for clinicians. An ECAA is generally defined as a dilation of the internal carotid artery (ICA) or common carotid artery (CCA) greater than 150% of the diameter of the normal healthy artery. The presence of an ECAA is usually found by coincidence in asymptomatic patients. Symptomatic patient may present with neurological dysfunction or symptoms of local compression. The initial diagnosis of ECAA is often by echo/duplex ultrasound imaging. However, Computerized tomographic angiography (CTA), with 3-dimensional reconstruction of the images (3D) can provide additional and valuable information, especially when considering surgical exclusion of the aneurysm. Recently, vessel wall imaging using contrast enhanced Magnetic Resonance with gadolinium administration was explored, which could potentially provide valuable information regarding aneurysm wall changes during clinical follow up. Location and accessibility of an ECAA is key information when considering the appropriate treatment. With the lack of evidence-based treatment guidelines, a conservative approach with or without medicinal treatment is currently the standard of care for asymptomatic non-growing ECAA. Open surgical repair has long been the accepted treatment for patients with a growing aneurysms or aneurysm related symptoms. Endovascular interventions are increasingly applied, especially when surgical intervention is considered too risky or not possible due to patient comorbidities or anatomical restrictions. Data on the natural course, immediate and long-term results of surgical or endovascular therapy is scarce. Thus, there is a clear need for an international collaboration collecting data of ECAA within a registry.

INTRODUCTION

Extra-cranial carotid artery aneurysm (ECAA) is a rare vascular diagnosis that accounts for less than 1% of peripheral aneurysms.[1] ECAA's are more common in men with a male to female ratio of 2:1 and the mean age at presentation around 50 years (range 35-68 years).[2] The most common definition of an ECAA is a dilation of the carotid artery greater than 150% of the diameter of normal (uninvolved) internal carotid artery (ICA) or common carotid artery (CCA). Bilateral ECAA have been reported in 13% of the cases and 15-20% of patients with an ECAA have multiple aneurysms (predominantly intracranial).[2] Current knowledge on ECAA is limited and is based on small case series and case reports lacking long term follow up.[2] Presentation of an ECAA depends on the etiology, location and size. The natural course of an ECAA remains uncertain but is believed that they rarely remain asymptomatic if they keep enlarging.[3] On the other hand; it is believed that non-growing ECAA will remain asymptomatic. Symptoms may include a palpable pulsating mass, peripheral nerve dysfunction, stridor, voice changes due to local compression, transient ischemic attacks (TIAs) or ischemic stroke. Morphologically there are two distinct types of carotid aneurysms, which are most often located in the internal carotid artery (ICA). The dilatation may be focal and saccular or fusiform and extensive. ECAA can be true or false aneurysms with the true aneurysms being caused by atherosclerosis, infection (HIV, tuberculosis Syphilis and Salmonella), arteritis, Marfan syndrome, fibro-muscular and medical degeneration. A false aneurysm or pseudo-aneurysm can be caused by trauma, iatrogenic, post carotid endarterectomy and post dissection. A recent histological analysis revealed two distinct types of ECAA, degenerative and dissection aneurysms with several inflammatory cells being found in some of the degenerative aneurysms.[4] A recent review described 281 published articles describing the management of ECAA.[2] Although several treatments

have been developed over the last years, for any etiology, the preferred treatment is yet unknown due to the rarity of the lesion and the lack of evidence-based guidelines.

Diagnosis

The purpose of imaging is to identify and confirm the presence of an ECAA, classify the ECAA, and to assess the anatomy in order to plan a possible surgical intervention. Further, imaging can be applied to evaluate possible aneurysm growth during follow up. Aneurysms are mostly diagnosed with echo/duplex ultrasound imaging but additional computed tomography angiography (CTA) with 3-dimentional (3-D) reconstruction of the carotid arteries (Figure 1) seem to contribute to the diagnosis and therapeutic work up.[5] CTA provides additional information on location and especially accessibility, thus allowing the surgeon/interventionist to decide which intervention is appropriate when an intervention is indicated.

Aneurysm volumetry using 3D images have been suggested to be of additional value next to diameter measurement for detecting changes in abdominal aneurysms.[6] This volumetry method to detect aneurysm growth could be used in the future for detecting ECAA changes and possibly predict the clinical course of an ECAA. More sophisticated imaging using 3Tesla high-resolution contrast enhanced Magnetic Resonance Imaging (3TMRI) with gadolinium administration is currently being investigated for vessel wall imaging. It is hypothesized that administering gadolinium during MRI results in enhancements of sites with inflammation[7], which could also be a marker for aneurysm growth. Also, in patients undergoing surgical resection the histological correlation of aneurysm wall enhancement with gadolinium and the degree of aneurysm wall inflammation could be investigated.

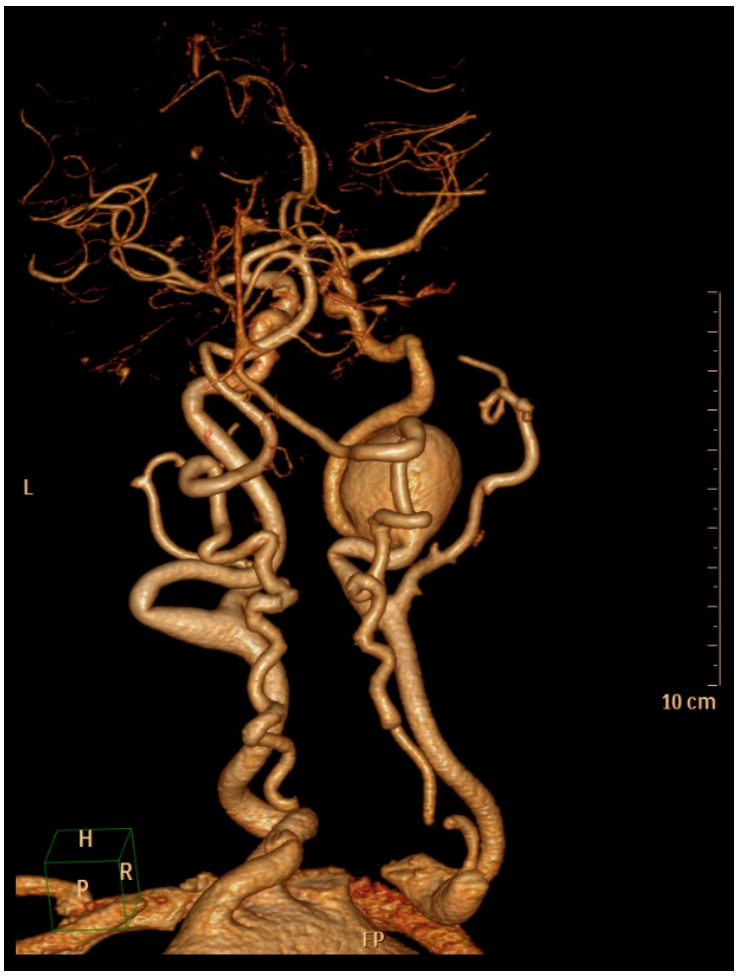

Figure 1. 3D CTA of a saccular aneurysm of the ICA.
3D: 3-dimesional, CTA: Computerized tomographic angiography, ICA: Internal Carotid Artery

Treatment options

Current management of an ECAA is based on the clinical presentation, etiology and location of the aneurysm.[8] Treatment aims to relieve symptoms and/or prevent complications such as intra-cerebral thrombo-embolic events or pharyngeal compression. The treatment strategies currently available are conservative and interventions with an open surgical approach, an

endovascular treatment or a hybrid approach, which combines an open and endovascular approach.[8] The conservative approach (antihypertensive medication, statin therapy and/or antiplatelet therapy) may be appropriate in asymptomatic non-growing aneurysms, inoperable cases and patients with life limiting comorbidities. However, very little data are available on the natural follow-up of asymptomatic patients. Currently patients with a symptomatic ECAA are considered best treated by invasive treatment. Surgeon/interventionist experience certainly plays a role in the type of treatment offered to the patient. Surgical resection of the complete aneurysm sac with direct reconstruction or an interposition graft to restore the blood flow is currently the gold standard .[1-3,5] Access to the internal carotid artery (ICA) is the most important factor in planning a surgical intervention. The location of an ECAA has been used in different classifications. Most studies refer to the cervical vertebrae to indicate the ECAA location. The Bouthillier classification describes the cervical part as C1, the petrous part as C2 and the intracranial part as C3-C7.[9] According to the classification of Attigah and Malikov this line of Blaisdell is used to determine if accessibility can be achieved. This line is a "virtual" line between the mastoid and the mandible angle. If the carotid artery is located above this line it is considered less accessible by a standard surgical approach, making alternative exposure techniques and/or endovascular assistance necessary.[10,11] Operative resection of an ECAA with or without arterial replacement graft has been associated with the risk of stroke and cranial nerve damage.[2] A recently published review, although based on small series, demonstrated low stroke numbers in both surgical and endovascular treatment group.[2]

Treatment option: surgery

If there is any doubt about accessibility of the distal ICA, the surgeon must decide whether certain additional procedures (e.g. mandibular subluxation)

are necessary preoperatively. Most surgeons perform carotid aneurysm surgery with the patient under general anesthesia. With the patient's neck slightly extended and rotated, the surgeon can gain access to the carotid bifurcation, internal jugular vein and the ICA by careful dissection, paying special attention to the hypoglossal and the vagus nerve. Vascular clamps can obtain proximal and distal carotid control but, in the case of distal aneurysm extension, a Fogarty catheter might also be helpful. Before the artery is clamped, the patient should be systemically heparinized to prevent thrombotic occlusion. Perfusion of the brain could significantly decrease by temporary clamping the carotid artery; therefore an intraluminal shunt may be used either in a standardized fashion or selectively when based on intraoperative neuromonitoring.[12] After gaining access to the ECAA one of these options may follow; 1) ECAA resection with ligation of the proximal (inflow) and distal (outflow) part of the extracranial ICA, 2) bypass without resection and 3) resection of the aneurysm with direct or indirect reconstruction of the blood flow.[8] Sir Astley Cooper was the first to perform ligation of the carotid artery and it is still performed in selected cases such as patients with a ruptured or mycotic an ECAA.[8,13] Although ligation is associated with an increased risk of stroke, it is believed that it can be safely performed if the backpressure in the carotid stump exceeds 70mmHg, suggesting an intact contralateral blood flow and an intact circle of Willis.[5] In some cases, an aneurysm cannot be resected, due to the large size, extension towards the base of the skull or because of adherence to adjacent structures. In these cases, it may be possible to balloon occlude the aneurysm and then bypass the aneurysm by creating an extracranial-intracranial (EC-IC) bypass. By not excluding the aneurysm from the circulation, the ECAA could still cause neurological symptoms due to embolization.[14] Following complete resection of the ECAA; the ICA can be reconstructed in different ways. In case of an elongated carotid artery adjacent to the ECAA (as in figure 1), it is possible to perform an end-to-end

anastomosis, or the external carotid artery can be used as a proximal transposition site (Figure 2).[5] Another reconstruction method is using an autologous saphenous vein as a graft to create an interposition bypass. If a vein is unavailable, a polytetrafluoroethylene (PTFE) or Dacron interposition graft can be used. An end-to-end or end-to-side anastomosis can be made between the native artery and the graft. Partial resection of an aneurysm can be performed in selected cases, when complete resection is not possible. Placing a patch or direct closure can repair the remaining defect. This method should be considered as the last option, because it leaves a part of the aneurysm wall behind which is prone to dilation and thrombus accumulation.[14]

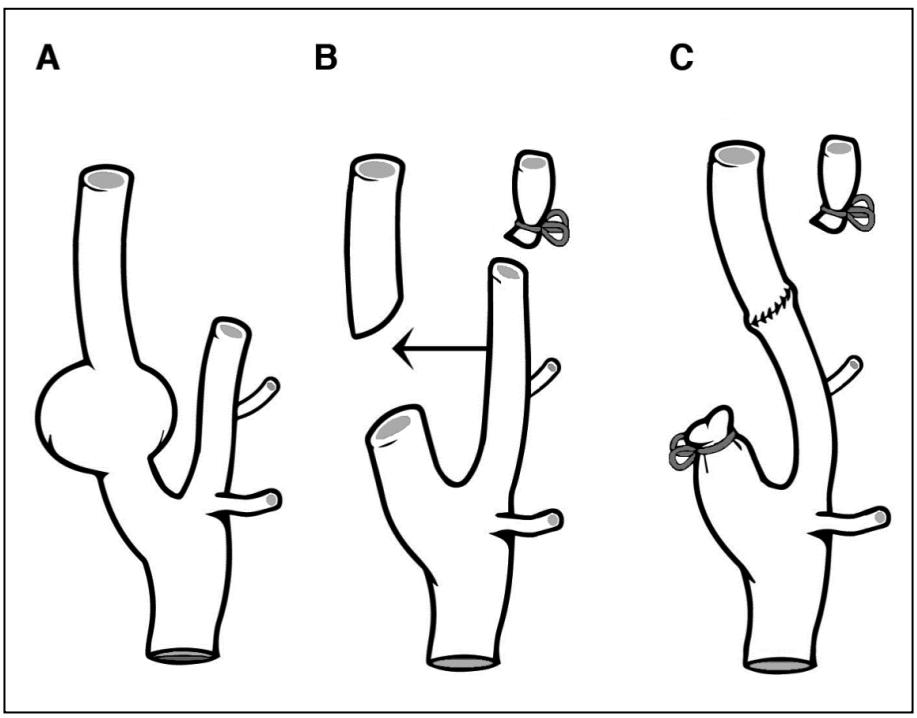

Figure 2. Aneurysm resection with transposition of the ECA to ICA.
A) ECAA located in the ICA. B) Resection of the aneurysm and ligation of the distal ECA. C) Transposition of the proximal ECA to the distal ICA and ligation of the proximal ICA. ECAA: Extracranial carotid aneurysm, ICA: internal carotid artery.

Treatment option: endovascular

Stent placement instead of surgical treatment can be considered in patients with comorbidities that make surgery too risky. Endovascular treatment is also favorable in patients with a "hostile neck" due to e.g. radiation, patients who have had previous surgery in the neck area or when the aneurysm is considered to be inaccessible (above the Blaisdell line). Endovascular procedures are typically performed under local anesthesia. Access to the ICA is obtained through a percutaneous common femoral artery puncture. An alternative approach is through a direct puncture of the proximal common carotid artery (CCA). A cerebral protection device may be deployed in the distal ICA to prevent embolization complications. When placing the stent, it must cover the entire aneurysm with the proximal and distal landing zones on "lesion-free" arterial wall to secure a "healthy-to-healthy" bridge. Stent choice depends on the arterial anatomy and aneurysm characteristics. Different stents are available including bare metal stents, balloon-expendable stents, self-expandable stents, covered stents and tapered and non-tapered stents. Self-expandable stents are mostly applied in stenotic carotid artery lesions. Bare-metal stents are usually the stent of choice for ECAA. They alter the blood inflow resulting in thrombosis of the aneurysm and at the same time preserving the vessel patency. Bare-metals stents (BMS) can also be used in combination with coil embolization if complete embolization with a BMS alone does not occur.[5, 15,16] Detachable coils are inserted into the aneurysm with a micro-catheter that is placed through the struts of the uncovered stent. These coils obstruct the blood inflow in the aneurysm cavity, which induces thrombus formation.[5] In non-branching arteries, wide-necked aneurysms and pseudo-aneurysms a covered stent can be used. These stents might reduce the risk of embolization during the procedure by trapping debris in the aneurysm sac that would otherwise protrude through the orifices of a bare-metal stent.[16] A

disadvantage of covered stents is the need for a large delivery system, making the procedure technically challenging.[5]

Flow diverting stents are a more recent development in stent designs. These laser-cut stents are designed to alter blood flow in the longitudinal axis (Figure 3). Like BMS, flow diverters promote thrombosis in the aneurysm sac and have been described to be effective in the exclusion of intracranial aneurysms.[17] One recently published case report described the successful treatment of an ECAA with a flow-diverting stent without any procedural or follow up complications.[17]

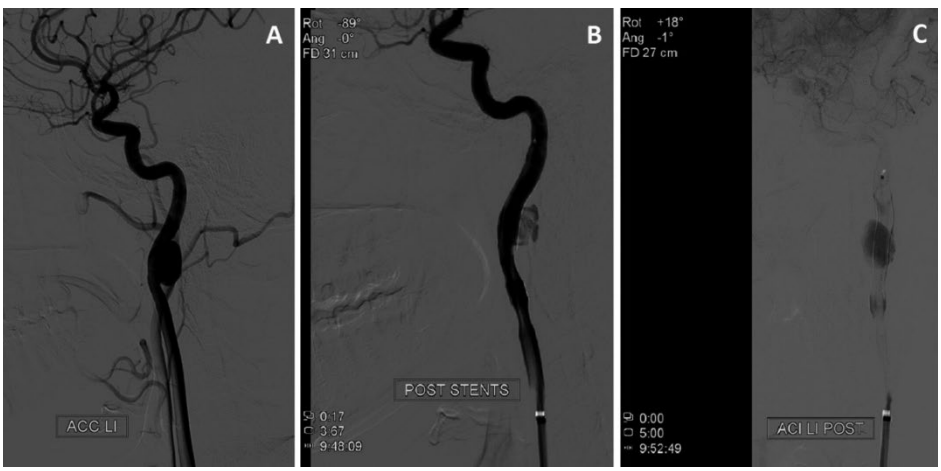

Figure 3. Flow diverting stent. A) Angiogram of the left ICA with an ECAA-prior to stenting. B-C) Angiogram post stenting with reduced flow in the aneurysm.
ECAA: Extracranial carotid aneurysm, ICA: internal carotid artery.

Treatment option: hybrid approach

A seldom performed procedure is the hybrid approach, which combines open surgical exposure of the proximal CCA and endovascular stent placement. During this procedure kinking and arterial loops that hinder endovascular stent placement, can be removed (Figure 4). Resection of the artery loop is followed by an arterial anastomosis (or anastomosis is made after stent placing), then a

stent is placed in the more distally located ECAA.[15] This approach has been performed on distally located ECAA with proximal loops or kinks according to a recent published case series.[15] No procedural complications like cerebral ischemia occurred and no deaths or strokes were reported within 30 days of intervention. These patients had no local or neurological symptoms during follow up, demonstrating good clinical and technical results of the hybrid procedure with placing bare metal.[15]

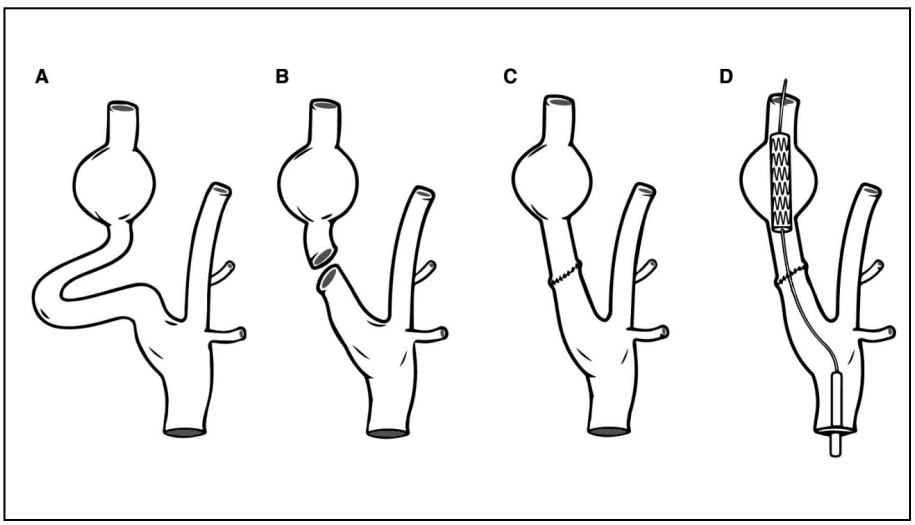

Figure 4. Hybrid approach. A) Aneurysm located in the distal ICA. B) Resection of a loop in the ICA. C) Primary end-to end anastomosis. D) Endovascular stent placement over the ECAA. ECAA: Extracranial carotid aneurysm, ICA: internal carotid artery.

Treatment option: endovascular embolization

The placement of a coil in an aneurysm sac as a treatment for an ECAA or any other peripheral aneurysm is rarely performed. During the procedure, a micro-catheter is passed through the neck of the aneurysm where the coil will be placed, which has a high risk of coil migration. Therefore, coils are used in combination with a bare metal stent. Percutaneous thrombin injection in the

aneurysm, a treatment applied to pseudo-aneurysm in the femoral artery, is considered technically difficult and too risky in ECAA because of the mostly fusiform shape of ECAA and the possibility of thrombin migrating into the intracranial system causing ischemic complications.[18]

DISCUSSION

ECAA is a rare condition and if left untreated or not treated on time when indicated, it may cause serious morbidity. Little is known about the natural course of both asymptomatic and symptomatic ECAA. Further, several treatment options exist but there is no clear guidance on the optimal type of treatment. Imaging modalities like aneurysm volumetry with a CT scan and the correlation between MRI and the histology of an aneurysm are believed to help predict the natural course of an ECAA. Future studies with long term follow up are needed to demonstrate if these imaging modalities can help physicians to decide whether an aneurysm should be treated or not. However, with the lack of evidence-based treatment guidelines physicians are faced with a therapeutic dilemma. Therefore, a web-based international registry has been designed to collect data on ECAA (www.cartoidaneurysregistry.com).[19,20] This registry opts to prospectively analyze the available data of both conservative and invasively treated ECAA in one and five years' time.[20] Subsequently, physicians could be accurately advised which patient with an ECAA should be treated and how.

CONCLUSION

There is no evidence-based guidance to indicate which patient needs to be treated nor is there an unequivocal recommendation for the optimal type of treatment for ECAA. A conservative strategy may be warranted for the asymptomatic, non-growing aneurysms, with or without medication. The current treatment of choice for symptomatic or growing aneurysm is surgical repair, with resection of the aneurysm and reconstruction of the blood flow the considered gold standard. Endovascular techniques with stent placement for exclusion of an aneurysm is the accepted alternative treatment for patients that cannot undergo surgery due to different comorbidities, high risk of complications, or patients with anatomical variations. The optimal treatment of patients presenting with ECAA is yet to be investigated. Important insights may be gained within a few years with the help of an international multicenter registry on this pathology.

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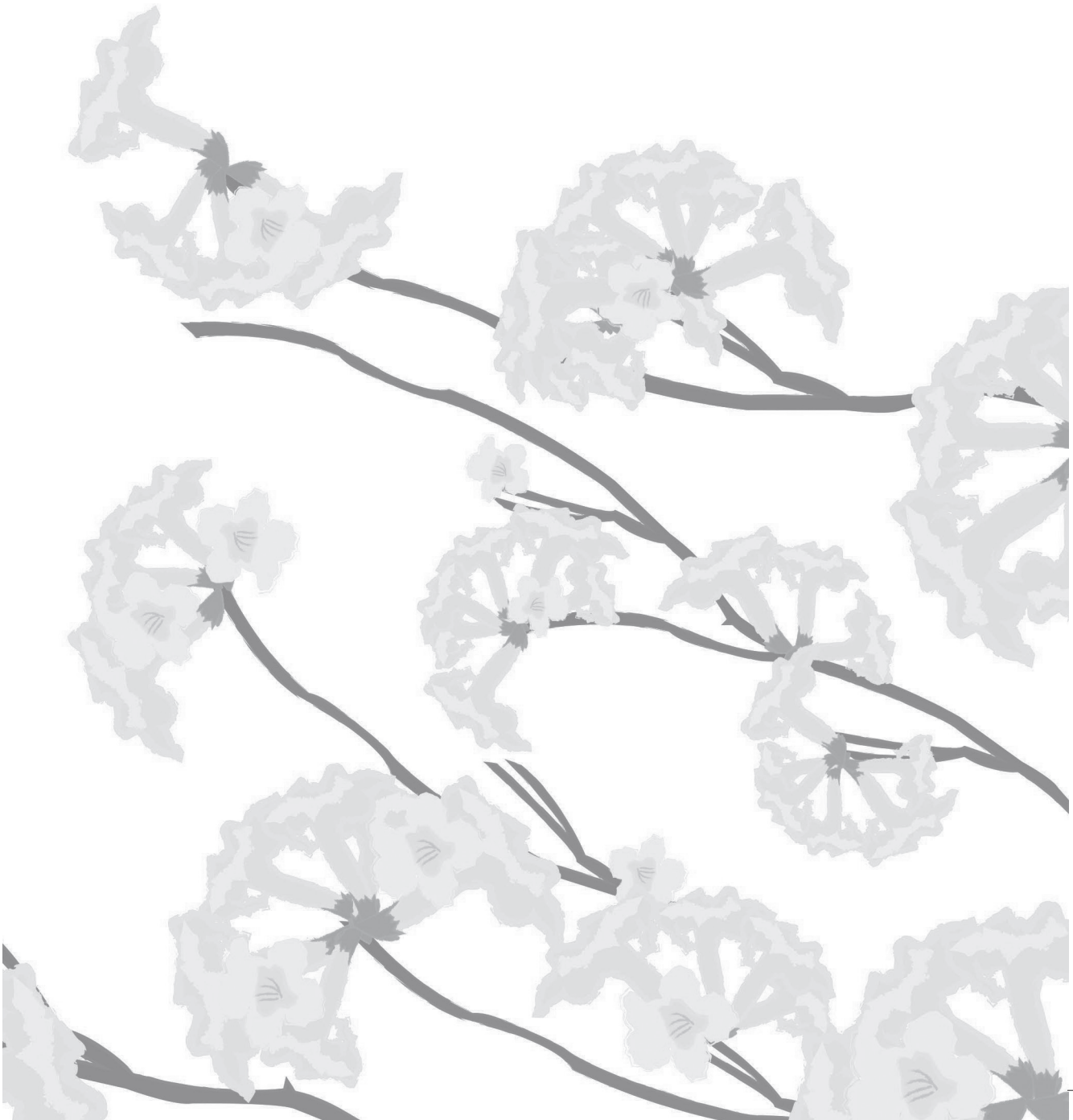
Chapter 10

Summary and General discussion



Extracranial carotid artery aneurysms (ECAA) are infrequently seen and with an unknown incidence. The underlying etiology are mostly atherosclerosis and dissection.[1] Because of the rarity little is known about its natural clinical course, optimal treatment and its association with other aneurysms in other vascular beds. The reported average age of patients with an ECAA is 50 years.[2] The outcome for these relatively young patients if left untreated is unknown, therefore, a better understanding of the natural clinical course, optimal work-up and treatment of ECAA is necessary.

Prevalence

ECAA is reported to compromise <1% of all peripheral aneurysms.[3] Because they are mostly found incidentally the majority have a silent clinical course.[3] It is therefore believed that they could be more prevalent. In order to study the prevalence and also the possible association with other vascular aneurysms, we studied the co-prevalence of ECAA in patients with an intracranial aneurysm. About 2-4% of patients with an intracranial aneurysm (IA) seem to also have an ECAA (Chapter 2-3). This is based on retrospective research with incomplete imaging of the carotid arteries, suggesting that ECAA may be even more prevalent. In chapter 3 we showed that the prevalence is almost three times higher with complete imaging of the internal carotid artery as compared to partial imaging just below the base of skull, revealing that the majority of ECAA is located in the mid segment of the extracranial part of the ICA.

Etiology and clinical course

The etiology of ECAA is diverse, however the majority are reported to be caused by atherosclerosis and dissection.[1] The changes in the vessel wall that trigger the formation of an ECAA remain unclear.

Also, different inflammatory cells have been observed in the walls of these aneurysms.[1] The autonomic nervous system is known to influence various

inflammatory processes and diseases.[5,6] Therefore, we explored whether changes of nerve fiber density occurred in ECAA and another muscular artery, namely popliteal artery aneurysms (PAA) and compared them to healthy arteries of both groups (Chapter 4). ECAAs showed a non-significant higher overall nerve density as compared to PAAs. Healthy carotid arteries showed a higher nerve density then the popliteal arteries. Also, ECAA had a non-significant higher density of scattered nerve fibers then the healthy carotid arteries. This suggests that outgrowth of nerve fibers from pre-existing bundles may be related to inflammation and aneurysm formation. However, we can only speculate about this, since this study was limited by a small sample size. This is due to the rarity of ECAA, the small number of patients undergoing surgical treatment for ECAA, and as a consequence the small number of ECAA tissue samples in our biobank.

Another method for visualizing inflammation in aneurysms is administration of gadolinium during MRI.[6] This results in enhancements of sites with inflammation[7], which could also be a marker for vessel wall changes and aneurysm growth. In Chapter 5 we investigated whether Gadolinium enhancement was present in patients with an ECAA being treated conservatively. Gadolinium enhancement was present in the majority of ECAA, when using a binary scale. This imaging method therefore seems like a useful tool to study arterial wall behavior over time in patients with ECAA, however future studies are needed to study the degree of enhancement.

It is believed that most ECAAs have a silent clinical course, but the risk of thrombo-embolization and subsequent stroke has yet to be elucidated.[7,8] Micro-embolic events in patients with carotid artery disease have been described to be subclinical. We investigated whether microvascular cerebral damage was visible in ECAA patients, seen as white matter lesions (WML) on MRI. The presence of WML has been described to be correlated with

increased future cerebrovascular risk and cognitive decline over time.[8] These WML were present in most asymptomatic ECAAs (chapter 5). However, it was also seen in all patients on the contralateral side of the ECAA. The questions remain whether a visual scale for the assessment of WML is a reliable test, if the presence of WML a part is of a systemic disease and if it will remain stable or increase over time.

Increased arterial tortuosity has been suggested as a predisposing factor for carotid artery dissection, which is an important etiological risk factor for development of ECAA.[9-11] To investigate the arterial tortuosity, we compared (Chapter 6) four different software packages for semi-automatic tortuosity measurements. All four had reproducible and comparable measurements, with an acceptable interobserver agreement, and are all therefore valid for measuring tortuosity.

Treatment

The clinical natural course is yet to be investigated in larger prospective studies. Our retrospective case series (Chapter 7) showed that patients with an asymptomatic ECAA have a rate of ischemic stroke in the aneurysm territory of 1.1 per 100 patient years. Most aneurysms do not grow over time and remain asymptomatic. Chapter 8 reports the results of a systematic review that was performed to summarize all the available data on the treatment of ECAA. The review shows clearly the lack of evidence and treatment guidelines. A total of 1816 patients with 1921 aneurysms were found, reporting on ECAAs caused by various etiological factors. The majority of the published data on ECAA report the surgical treatment and short-term outcome of symptomatic ECAA.

There is no evidence-based guidance to indicate which patient needs to be treated nor is there an unequivocal recommendation for the optimal type of treatment for ECAA. A conservative strategy may be warranted for the asymptomatic, non-growing aneurysms, with or without medication. The

current treatment of choice for symptomatic or growing aneurysm is surgical repair, with resection of the aneurysm and reconstruction of the blood flow the considered gold standard (chapter 9). Endovascular techniques with stent placement for exclusion of an aneurysm is the accepted alternative treatment for patients that cannot undergo surgery due to different comorbidities, high risk of surgical complications, or in patients with anatomical variations. The optimal treatment of patients presenting with ECAA is yet to be investigated. Important insights may be gained within a few years with the help of an international multicenter registry on this pathology.

Future perspectives

Full imaging of the carotid tree is necessary to determine whether ECAA are associated with IA. Future research should also investigate whether grading of vessel wall enhancement with gadolinium on MRI is associated with ECAA disease activity and growth. Also, the challenge is to develop new imaging techniques to determine ECAAs disease activity and its effect on the brain. It should be considered to investigate if white matter lesions seen in ECAA patients remain stable or increase over time. This could in the future influence the treatment of asymptomatic ECAA.

Further research should also investigate whether arterial elongation and tortuosity are indeed associated with ECAA. If increased arterial tortuosity would exist in ECAA patients, it may aid in individual patient's risk prediction for adverse outcome. To get the answer, we will analyze data from the prospective CADISP study group to study the development of ECAA in patients with a proven extracranial carotid artery dissection and differentiate for level of tortuosity as compared to patients from a trauma screening cohort.

Also, blood samples collected from the ECAA biobank will be useful for multiple researches in the future.

With the ongoing lack of evidence-based guidelines on the approach of patients with an ECAA, the online registry (www.carotidaneurysmregsitry.com) will continue to prospectively collect data of patients to help address future diagnostic and therapeutic questions.

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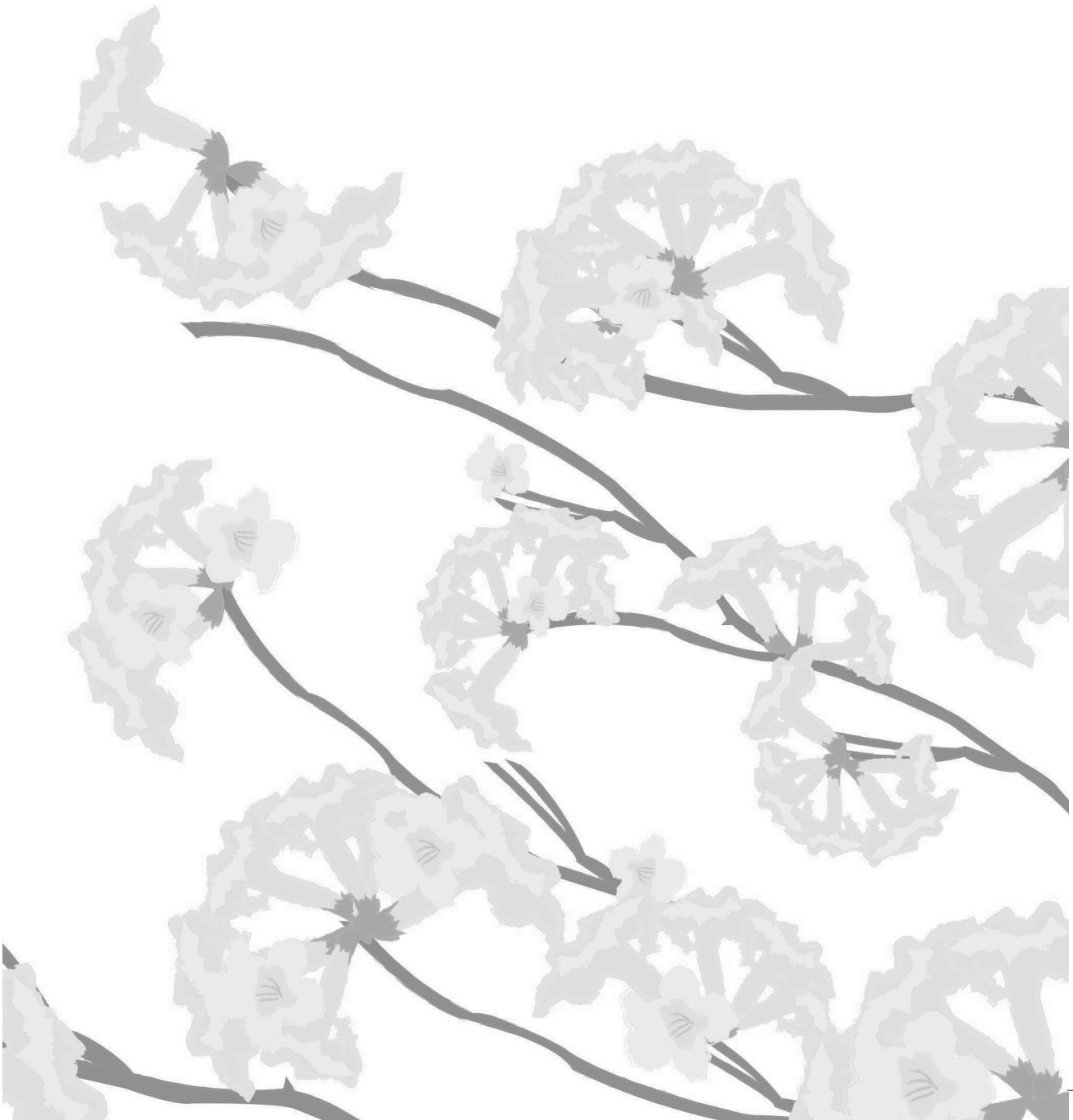
Chapter 11

Nederlandse samenvatting



Het extracraniële aneurysma van de arterie carotis (ECAA) is een zeldzame aandoening. De meest voorkomende oorzaak is atherosclerose en dissectie.[1] Omdat het zo zeldzaam is, is er ook weinig bekend over het natuurlijk beloop, de beste behandeling en associatie met aneurysmata elders in het vaatbed. De gemiddelde leeftijd van patiënten met een ECAA is ongeveer 50 jaar.[2] Om het beloop, prognose en de beste behandeling bij deze relatief jonge patiënten beter in kaart te brengen, is meer onderzoek nodig.

Prevalentie

Minder dan 1% van alle perifere aneurysmata is een ECAA.[3] ECAA worden meestal per toeval ontdekt en zijn doorgaans asymptomatisch.[3] Mogelijk komen ECAA vaker voor dan wat de literatuur beschrijft ten gevolge van onderrapportage en non systematische screening van hoog risico populaties. Om dit te bestuderen en om te onderzoeken of ze geassocieerd zijn met andere aneurysmata, hebben we in Hoofdstuk 2 en 3 de prevalentie van ECAA bij patiënten met een intracranieel aneurysma (IA) onderzocht. Ongeveer 2-4% van patiënten met een IA hebben ook een ECAA blijkt uit onze retrospectieve studie van patiënten met incomplete beeldvorming van de arterie carotis. Dit suggereert dat de prevalentie mogelijk hoger is. In Hoofdstuk 3 zien we ook dat de prevalentie bijna drie keer hoger is bij complete beeldvorming van de arterie carotis in vergelijking met incomplete beeldvorming. Deze studie laat ook zien dat de meeste ECAA zich bevinden in het middelste segment van de extracraniële arterie carotis interna.

Etiologie en klinisch beloop

De etiologie van ECAA is divers, maar de belangrijkste oorzaak van ECAA is atherosclerose en dissectie.[1] De veranderingen in de vaatwand die het ontstaan van een aneurysma tot gevolg hebben zijn nog onduidelijk. Uit eerdere onderzoek blijkt dat ontstekingscellen aanwezig zijn in de vaatwand

van aneurysmata.[1] Volgens gepubliceerde onderzoeken heeft het autonome zenuwstelsel invloed op meerdere ontsteking- en ziekteprocessen.[5,6] In Hoofstuk 4 hebben de mogelijke invloed van het zenuwstelsel onderzocht door te kijken naar veranderingen in de dichtheid van zenuwbundels en vezels in de vaatwand van ECAA. We hebben deze vergeleken met een andere musculaire arteriën met een aneurysma, de arterie poplitea. Deze twee groepen werden ook vergeleken met gezonde arterie carotis en poplitea. ECAA blijkt een niet-significant hoger zenuwbundel dichtheid te hebben ten opzichte van poplitea aneurysmata. De gezonde arterie carotis heeft ook een niet-significant hoger zenuwbundel dichtheid dan de gezonde arterie poplitea. ECAA bleken ook een niet-significant hogere dichtheid van zenuwvezels te hebben in vergelijking met de gezonde arterie carotis en poplitea. Dit suggereert dat uitgroei van zenuwvezels mogelijk geassocieerd is met inflammatie en aneurysmavorming. Echter, harde uitspraken hierover kunnen niet worden gedaan omdat het om een zeer klein onderzoek gaat met weinig patiënten. Dit komt door de zeldzaamheid van de ziekte en omdat er weinig patiënten geopereerd worden. Dit resulteert in een beperkt aantal beschikbare weefsel samples voor onderzoek vanuit onze vasculaire biobank de Athero-Express.

Een andere methode om inflammatie te objectiveren in aneurysmata is door gadolinium contrast toe te dienen tijdens een MRI-scan. [6] Dit resulteert in opname van gadolinium in weefsel met inflammatie. [7] Gadolinium zou als een marker kunnen functioneren om vaatwand veranderingen en groei in aneurysmata te visualiseren. Hoofdstuk 5 beschrijft Gadolinium opname in ECAA-vaatwand bij patiënten die conservatief zijn behandeld. De meeste ECAA hadden Gadolinium opname in de vaatwand. Deze MRI-techniek zou in de toekomst wellicht toegepast kunnen worden om de vaatwand veranderingen in de loop van de tijd verder te kunnen onderzoeken.

Hoewel de meeste patiënten met ECAA asymptomatisch zijn, kunnen ze cerebrale embolieën ontwikkelen die leiden tot een TIA of een beroerte.[7,8]. In Hoofdstuk 5 hebben we onderzocht of asymptomatische patiënten met een ECAA wittestof afwijkingen hebben in de hersenen. Aanwezigheid van witte stofafwijkingen kan een teken zijn van micro-embolieën en stille hersenschade. De aanwezigheid van wittestof afwijkingen gaat gepaard met een verhoogd risico op beroerte in de toekomst en cognitieve achteruitgang.[8] De meeste patiënten met een ECAA in onze database hadden ipsilaterale wittestof afwijkingen. Echter, alle patiënten hadden in de andere (contralaterale) hersenhelft ook wittestof afwijkingen. De vraag of de visuele schaal om wittestof afwijkingen te bepalen betrouwbaar is en of wittestof afwijkingen deel uitmaakt van een systemische ziekte. Toekomstig onderzoek moet aantonen of het aantal wittestof afwijkingen in asymptomatische patiënten met een ECAA stabiel blijft of verder zal toenemen in de loop van de tijd.

Een toename van arteriële tortuositeit in de arterie carotis wordt beschreven als een risico factor voor het optreden van een dissectie. Dissecties zijn een van de meest voorkomende oorzaken van ECAA. [9-11] Om de arteriële tortuositeit te bepalen hebben we in Hoofstuk 6 vier verschillende software vergeleken die semi-automatisch de tortuositeit berekenen van de arterie carotis, in patiënten met een ECAA. Alle vier hadden een acceptabele inter-observer variabiliteit en kunnen dus gebruikt worden voor deze metingen.

Behandeling

Het natuurlijk beloop van ECAA moet nog onderzocht worden in prospectieve studies. Onze retrospectieve case series (Hoofstuk 7) heeft laten zien dat onbehandelde asymptomatische ECAA de kans op een beroerte heeft van 1.1 per 100 patiënten jaren en dat de meeste ECAA niet groeien en asymptomatisch blijven. Hoofstuk 8 beschrijft een overzicht van de literatuur

over de behandeling van ECAA. Deze review laat zien dat er in totaal 1816 patiënten worden beschreven met 1921 aneurysmata met verschillende etiologie. De meeste aneurysmata worden volgens de literatuur chirurgisch behandeld en beschrijven alleen korte termijn resultaten van symptomatische ECAA. Deze review laat duidelijk zien dat er nog gebrek is aan wetenschappelijke onderbouwing rondom de keuze van behandeling van ECAA.

Er is nog geen duidelijk richtlijn voor de behandeling van ECAA. Een conservatief beleid voor asymptomatische, niet groeiende aneurysmata, met of zonder medicatie wordt aangeraden. Bij symptomatisch en groeiende ECAA wordt chirurgische resectie met continuïteitherstel van de slagader aangeraden. Endovasculaire behandeling met het plaatsen van een stent wordt als alternatief gezien voor aneurysmata die slecht toegankelijk zijn voor een chirurgische ingreep en bij patiënten met een hoog risico op perioperatieve complicaties (Hoofdstuk 9).

De optimale behandeling van ECAA moet nog onderzocht worden. De resultaten van de internationale Carotid Artery Registry (CAR) www.carotidaneurymregistry.com zal in de toekomst leiden tot de richtlijnen voor de behandeling van ECAA.[12]

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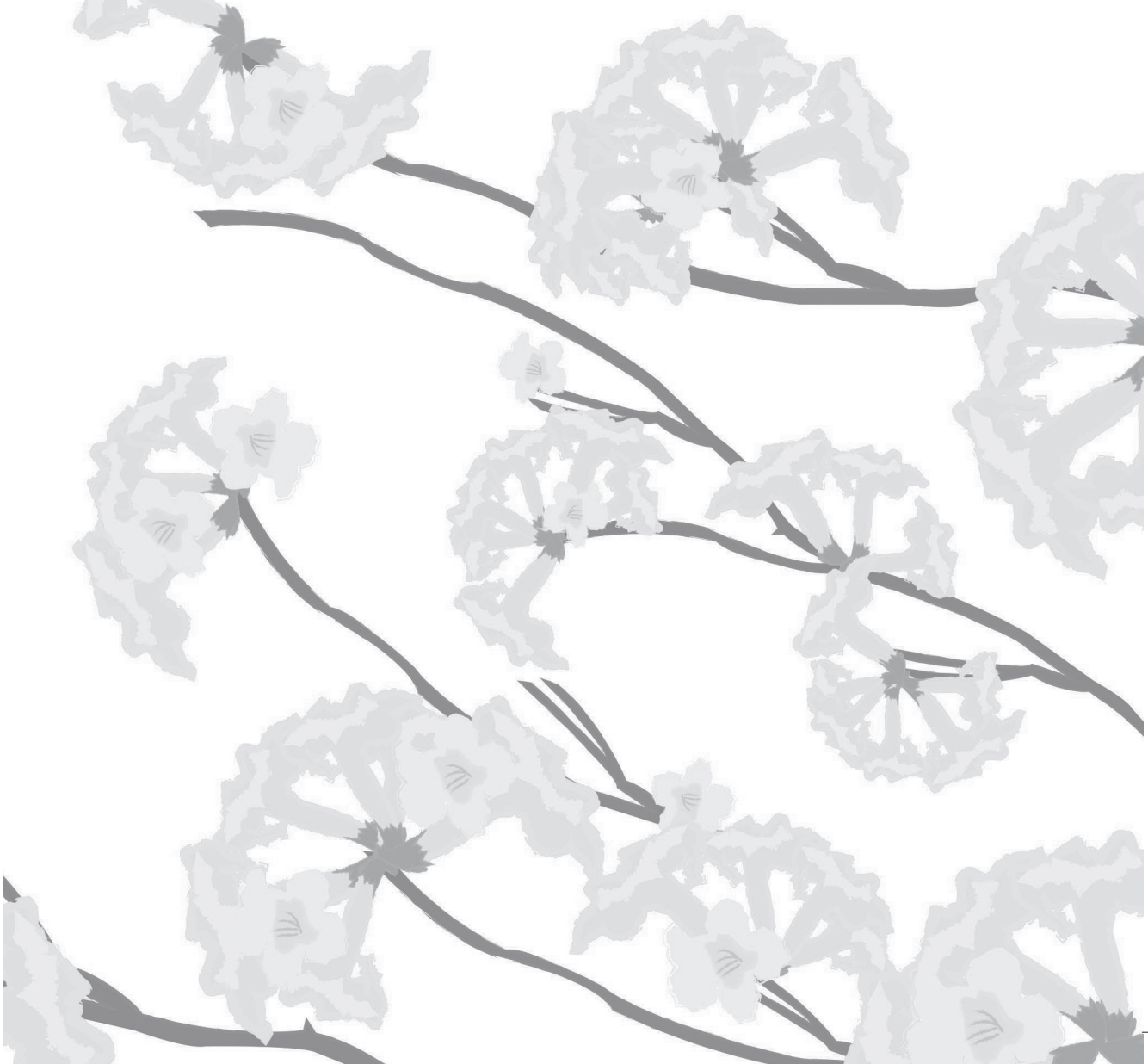
Chapter 12

Review committee

Acknowledgments/Dankwoord

List of publications

Curriculum Vitae



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Curriculum vitae

Vanessa Pourier was born on November 13, 1985 in Willemstad, Curaçao. After she graduated from secondary school she moved to the Netherlands to study medicine. In 2006 she started studying medicine at Utrecht University, the Netherlands and graduated in 2012. During internships, she developed her interest in surgery which led to opportunity to work as a resident in the surgical department at the University Medical Center Utrecht. During this time, she started doing research on the carotid arteries under supervision of Prof. dr. G.J. de Borst. This ultimately led to the opportunity to work as a PhD candidate, doing research on extracranial carotid artery aneurysms and coordinating the online Carotid artery aneurysm registry. She then returned to the clinic as a resident in the Slotervaart Medical Center in Amsterdam. Currently, she is working a resident in the surgical department of the Spaarne Gasthuis in Haarlem and Hoofddorp. In the near future she plans on applying for a position to start surgical training.