International Journal of Surgery 9 (2011) 177–182

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.theijs.com

Size and nature of emboli produced during carotid artery angioplasty and stenting: *In vivo* study

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ARTICLE INFO

Article history:
Received 28 May 2010
Received in revised form
26 October 2010
Accepted 3 November 2010
Available online 23 November 2010

Keywords:
Carotid artery angioplasty
Carotid artery stenting
Embolisation
Computed tomography
Calcium scoring
Electron microscopy

ABSTRACT

Aim: Microembolization continues to be a major risk for patients undergoing carotid artery stenting (CAS) of high-grade atherosclerotic carotid stenoses. Further insight into the characteristics and significance of these embolized particles was deemed necessary. We aimed to assess the size and composition of debris captured by filters during CAS and to determine if this could be predicted using standard imaging techniques.

Methods: 20 patients (10 symptomatic, 15 men, mean age 64.6 years) undergoing CAS for high-grade ICA stenosis were recruited. All underwent pre-operative CT angiography and calcium scoring. All underwent CAS using the same protocol. A filter-type embolic protection device (EPD) was used and retrieved post-operatively and captured particles underwent analysis using a Scanning Electron Microscope (SEM) for counting, sizing, and composition.

Results: Clinical. Debris was found on 100% of filters when analysed with SEM. There were non-significant trends for CAS in asymptomatic patients to produce a greater number of smaller, calcified particles while in symptomatic patients we observed larger, lipid-rich particles. When stratified according to pre-operative calcium scores, 'calcium-rich' plaques produced significantly greater numbers of emboli captured on the EPD ($p = 0.02$).

Conclusions: Filter-type EPDs collect debris of significant quantity and size during the CAS procedure as performed in our institution. The collected material was likely dislocated from the atherosclerotic plaque. CT calcium scoring allows us to predict the nature of material captured by the EPD. These data may allow the clinician to individualise care during CAS and thus reduce peri-operative risk.

1. Introduction

Carotid endarterectomy (CEA) has long been established as the standard treatment for symptomatic atherosclerotic stenosis of the internal carotid artery (ICA), although it does have an accepted complication rate.[1,2] The development of carotid angioplasty and stenting (CAS) as a minimally invasive treatment has joined surgery in centres with extensive experience and skilled interventionalists.[3,4] The rationale for carotid revascularization, surgical or endovascular, is to reduce the future risk of stroke. Unfortunately, carotid revascularization itself poses a risk of stroke, and enormous efforts have been made in refining both surgical and endoluminal techniques to reduce peri-procedural stroke risk.

The chance of ischaemic events due to peri-procedural micro-embolization is still a threat to those patients undergoing CAS. The advent of embolic protection devices (EPDs) was greeted with great enthusiasm for reducing the embolic risk. Nevertheless, although EPDs seem safe and effective, silent ischaemic lesions thought secondary to distal embolisation have been identified on diffusion-weighted imaging (DWI) by several authors.[5–11]

The morphology of the atherosclerotic wall has been the focus of general interest because it has been proved to have a pivotal role in plaque vulnerability.[12] The purpose of the current study was to describe the method and results of the electron microscopic analysis of filter content in protected CAS of severe ICA stenosis and to evaluate any correlation with pre-operative imaging using computed tomography (CT) calcium scoring. It was felt important

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1743-9191/$ – see front matter
doi:10.1016/j.ijsu.2010.11.004

to understand further the nature of the emboli produced during CAS procedures, and to gain further insight into the way that the filter-type EPD employed by our institution works.

2. Methods

Ethical approval was granted by a Local Research Ethics Committee (LREC) prior to this study commencing. Consecutive patients were given full verbal and written information about the research project prior to giving their written consent. It is our standard of care that all patients are reviewed pre-operatively by a neurologist and discussed at a joint surgical and neurological meeting before consideration for intervention.Symptomatic patients were defined as those with clinical symptoms of a cerebrovascular accident (CVA), transient ischaemic attack (TIA) or amaurosis fugax occurring within the last six months.

Patients who had smoked or who were currently smoking were considered in the smoking group. Those that were receiving drugs for control of hypertension were considered to be hypertensive.Patients with insulin-dependent and tablet-controlled diabetes were placed into the diabetic group. Those with a family history of vascular disease were considered to be patients with a 1st or 2nd degree relative that suffered a stroke or coronary artery disease below the age of 65.

Details of ischaemic heart disease (IHD) were obtained. Patients with a history of angina, myocardial infarction, coronary endoluminal intervention and coronary artery bypass graft (CABG) were considered to have a history of IHD.

2.1. Pre-operative CTA and calcium scoring of target vessel

Patients had CT angiography (CTA) of their supra-aortic and intracranial vessels prior to their revascularization procedure. This was performed routinely (on clinical grounds) to further characterise the stenosis, to determine whether or not the patients' anatomy was suitable for CAS, to identify 'tandem' lesions, and to aid in assessing whether those who might not be suitable for CAS would be at higher risk of requiring intra-operative shunting (from assessment of the circle of Willis) during their CEA.

Spiral CT angiography was performed with a 16 multi-detector row scanner (Phillips MX8000, Phillips). A standard protocol was used: 120 kV, 210 mAs, 3 mm section thickness, and 3 mm/s table feed. Volume acquisition typically covered the region from the aortic arch to *sella turcica* with a scanning duration of 32–40 s. Images were reconstructed every 1.5 mm, which resulted in 75–101 sections. Patients were asked to avoid swallowing, but quiet breathing was allowed throughout the examination.

Contrast material (Omnipaque 350, Amersham Health, UK) was injected intravenously with a power injector (Medtron Injektron CT2, Medizinische Systeme GmbH, Germany) through a 14G intravenous cannula sited in the right antecubital fossa. A volume of 120 mL at a rate of 3.5 mL/s was used. The mean delay between the injection of the contrast material and the initiation of spiral CT scanning was 18 s (range, 15–26 s).

In order to determine the degree of ICA stenosis data from the CT sections were transferred to a satellite workstation for image processing. The axial CT images were viewed for research purposes to determine the site of maximal carotid stenosis and the presence and volume of calcified plaques. Using the Maximal Intensity Projection (MIP) images, the narrowest point in the artery was measured and the stenosis graded according to NASCET criteria.[13]

Calcification of the carotid plaque was quantified using standardized CT software implemented in the scanner, with calcium defined as a radiation attenuating structure with a density of more than 130 Hounsfield units (HU) in an area of 0.5 mm^2. This allowed the collection of 3 data points for each plaque. These comprised the area of calcium (i.e. number of pixels covered by calcium when presented in 2 dimensions) at the site of maximum stenosis (Ca^{Max}), and the total area of calcium from all slices within the plaque (Ca^{Total}). The calcium score (Ca^{Score}) was calculated as the product of the lesion area and the cofactor 1–4 (cofactor 1, 130–199 HU; cofactor 2, 200–299 HU, cofactor 3, 300–399 HU, cofactor 4 $\geq$ 400 HU) at the maximum thickness of the lesion being measured.

For subsequent analyses it was decided that values for Ca^{Score} would be used for three reasons; firstly because this figure correlates well with Ca^{Max} and Ca^{Total}, secondly because the whole plaque (of which Ca^{Max} is the best measure) was subject to intervention, and thirdly for simplicity and clarity in presenting the results. The population were stratified into groups according to whether their Ca^{Score} was lower or higher than the mean value (288.08). This allowed a more straightforward analysis of whether pre-operative CT calcium scoring could predict the nature of particles captured on the EPD.

2.2. Carotid angioplasty and stenting procedure

This has been described previously.[14] Briefly, CAS was performed under local anaesthesia (20 mL 1% lidocaine) using access via the femoral artery in all cases. In most cases an 8F guiding catheter was used, having previously cannulated the external carotid artery. Heparin was administered to maintain an Activated Clotting Time (ACT) of 250–300 s. Patients remained awake during the operation enabling active, clinical monitoring of their neurological state. Routine physiological monitoring included pulse oximetry, electrocardiogram, and invasive blood pressure measurement via the radial artery. The procedures were performed by a team comprising a Consultant vascular surgeon, a Consultant radiologist, and a Consultant interventional cardiologist. Use of an EPD and dedicated carotid stenting system was universal – Carotid Wallstent™ and EZ FilterWire™ (Boston Scientific).

Fig. 1. Scanning electron micrograph of an Embolic Protection Device used during a CAS procedure in a patient with a symptomatic ICA stenosis.

2.3. Retrieval of embolic protection device

At the end of each procedure the EPD/filter was retrieved from the patient as per the manufacturer's instructions. The filter was then cropped from its delivery system and stored in 0.5% glutaraldehyde solution. The filters were then stored for batch analysis using electron microscopy (EM).

2.4. Electron microscopy of the EPD

The filters were fixed in 3% glutaraldehyde in cacodylate buffer (pH 7.2) and dehydrated through a graded series of ethanol baths. The filters were then critical-point dried from carbon dioxide, cut open to reveal the inner surface and mounted on aluminium stubs with double-sided adhesive discs. The specimens were sputter-coater with gold prior to examination in a Cambridge S-360 Scanning Electron Microscope (SEM). Digital images from the SEM were recorded using a Prism frame-grabber (Fig. 1) and the emboli counted (total number), sized (100–500 μm, 500–1000 μm, and 1000+ μm) along the major (or longest) axis and analysed for their composition (platelet aggregation/thrombus, calcium-rich material, amorphous material/lipid) by a single, experienced examiner blinded to the patients' symptom status.

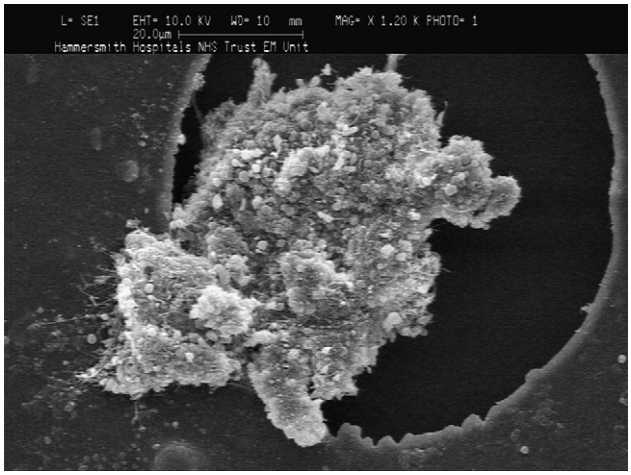

Fig. 2. SEM of a platelet aggregation seen on an EPD. Note that the circular 'window' it is adherent to is one of the pores that make up the filter; they have a diameter of only 100 μm.

Table 1
Demographics of the symptomatic and asymptomatic study groups.

Variable	Symptomatic		Asymptomatic		*p* value (*t*-test)
	N = 10	%	*N* = 10	%	
Age (years)	65.3 ± 14.3	–	63.8 ± 17.6	–	ns
Male gender	8	80	7	70	ns
Ipsilateral stenosis (%)	70.6	–	74.8	–	ns
Contralateral stenosis (%)	35.3	–	48.6	–	ns
History of hypertension	9	90	9	90	ns
History of smoking	8	80	9	90	ns
History of dyslipidaemia	9	90	8	80	ns
History of diabetes mellitus (IDDM or NIDDM)	2	20	1	10	ns
History of IHD (Previous angina/MI/CABG/PCI)	6	60	5	50	ns
Post-operative deficit	0	0	1*	10	ns

* = Ocular stroke.

A lower cut-off limit of 100 μm was used, since using the SEM enabled the examiner to observe many hundreds/thousands of very small particles which would have been prohibitive in terms of time, and questionable in terms of clinical significance (Fig. 2).

2.5. Statistical analysis

Continuous variables were expressed as mean ± SD. *P*-values ≤ 0.05 were considered statistically significant. Comparisons of demographics, risk factors and comorbidity data between treatment groups were made using the *t*-test. Analysis was conducted by using the statistical software SPSS version 15.0 for Windows (SPSS Inc, Chicago, IL, USA).

3. Results

20 patients undergoing elective procedures were entered into this study (Symptomatic = 10, Asymptomatic = 10). The demographics of each group are shown in Table 1.

One asymptomatic patient (5%) suffered a post-operative ocular stroke – this was confirmed by neurological and ophthalmic review and was permanent.

The only (non-significant) difference of note between the study groups are firstly the tendency to intervene on more severe ICA stenoses if the patient is asymptomatic (Fig. 3 - there is no evidence yet to support CAS in this group).

Table 2
Overview of results for SEM of filter-type embolic protection devices used during carotid artery stenting.

Pathological Feature	Filters (*n* = 20)	%
Macroscopic presence of debris	17	85
Symptomatic	9	90
Asymptomatic	8	90
Presence of debris on SEM	20	100
Mean number of particles per filter		
Symptomatic	15.8	–
Asymptomatic	9.8	–
Filters with particles 100–500 μm	20	100
Filters with particles 500–1000 μm	16	80
Symptomatic	9	90
Asymptomatic	7	70
Filters with particles >1000 μm	3	15
Symptomatic	2	20
Asymptomatic	1	10
Mean size of particles (μm)	203.05 ± 348.3	–
Symptomatic	274.8 ± 574	–
Asymptomatic	131.3 ± 158	–

3.1. Electron microscopy

SEM was attempted and successful in 100% of all cases. A summary of the pathological data is presented in Table 2.

The first observation to be analysed was of the total number of emboli captured by the EPD, as assessed using the electron microscope. There was a tendency for CAS in asymptomatic patients to produce more emboli, although this did not reach statistical significance (Fig. 4).

When the data are further stratified according to trapped particle size, there was a non-significant trend for CAS in the symptomatic patient to produce more particles that measured >500 μm. It was also shown, however, that CAS in the asymptomatic patients produced significantly more particles that measured <500 μm than the same in symptomatic patients (Fig. 5a and b).

The main constituent of each of the particles seen on the retrieved EPD was then assessed using the SEM (Fig. 6). In cases where the particle was heterogeneous in consistency, that part thought to make up >50% by volume was listed as the main particle type.

A significant trend for CAS in asymptomatic patients to cause calcium-rich particles to be trapped was noted (8 vs 2; $p < 0.05$) as was a tendency for the same in symptomatic patients to cause the production of lipid-rich particles (1.2 vs 5.2; $p < 0.05$). There were no statistically significant differences in the number of platelet aggregate/thrombus-type particles seen.

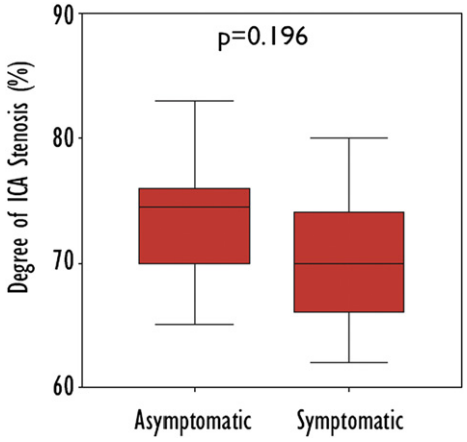

Fig. 3. A comparison of the degree of ICA stenosis (measured using NASCET criteria on CTA) between each study group.

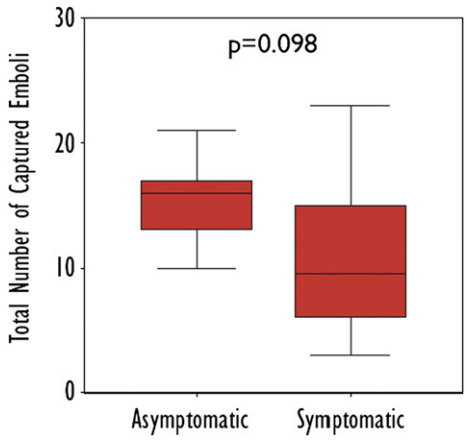

Fig. 4. Differences in total number of captured emboli according to symptom status of the patient.

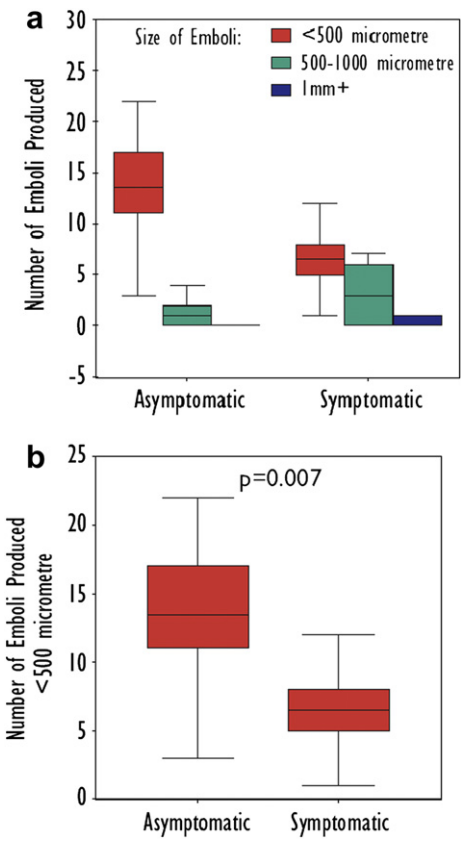

Fig. 5. a: Number and size of captured particles produced during CAS procedures in symptomatic and asymptomatic patients as assessed with SEM. b: CAS in asymptomatic patients allowed the EPD to capture significantly more particles sized less than 500 μm as assessed with SEM.

3.2. CT calcium scoring and observed debris

It was noted that those plaques identified as 'high density' with CT calcium scoring produced significantly greater numbers of emboli captured on the EPD ($p = 0.02$), that these were more likely to be approximately 500 μm in size, and of an increased likelihood that they consisted of calcium-rich material (p = ns). These results are displayed graphically in Fig. 7a–c.

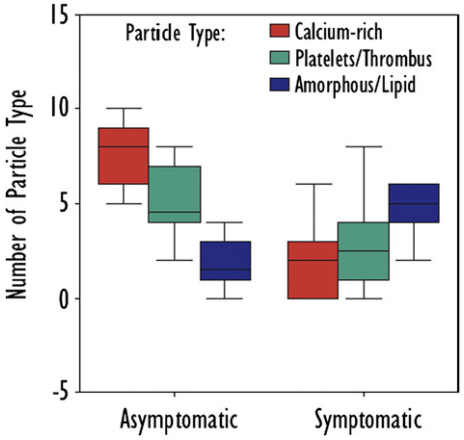

Fig. 6. Comparison of the particle types trapped by the filter-type EPD according to the symptom status of the patient.

4. Discussion

This study shows that filter-type EPDs can capture particulate emboli released during CAS (stent placement and EPD retrieval phases only) but not those before filter placement or after its retrieval; these microemboli can contribute to increase peri-procedural risk and should be taken into account when considering

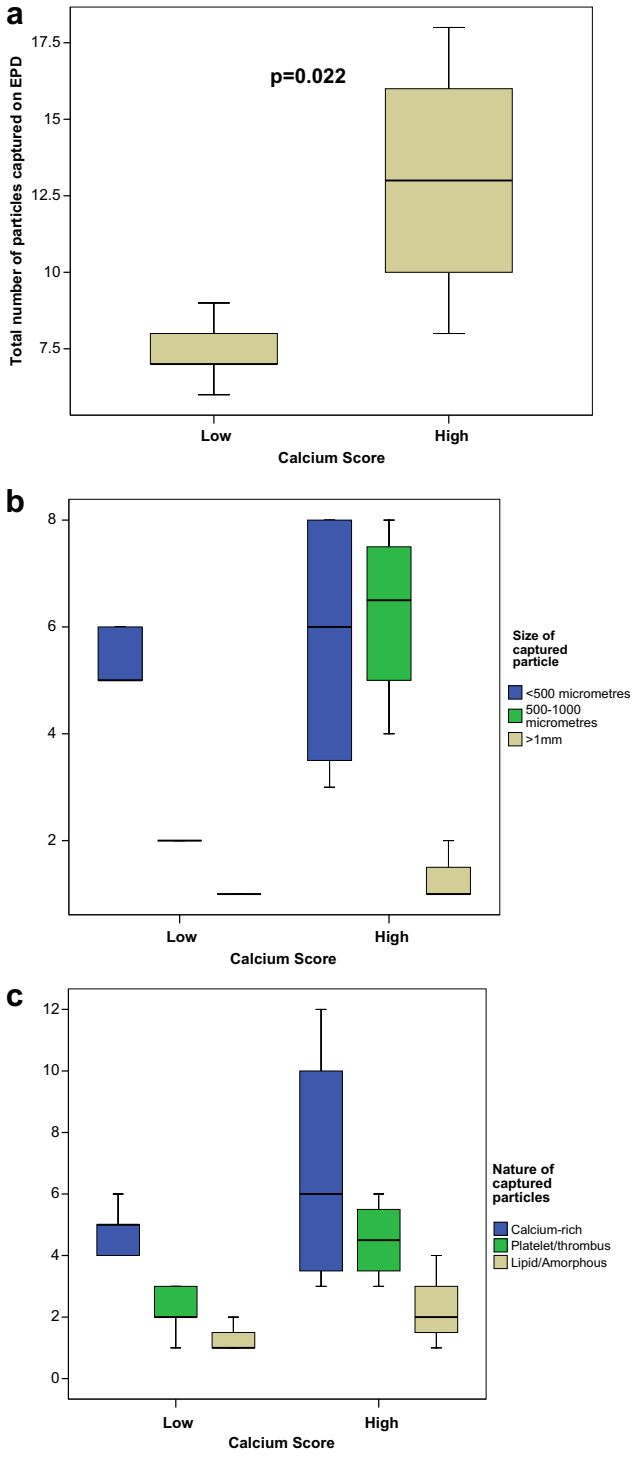

Fig. 7. a: Plaques identified with a 'high' calcium score produced significantly more emboli. b: There was a trend for highly calcified plaques to produce smaller particles. c: Such captured particles were more likely to be calcium-rich.

EPD choice. This is clinical confirmation of the data gained with filter protection during *ex vivo* experiments.[15,16] Debris was captured in 100% of procedures when assessed using SEM which agrees with the results of a similar study recently published,[17] compared with 83.7% and 77% impreviously published studies that performed histological analysis of captured particulate debris,[18,19] and 60.5% when visually inspecting the used EPD.[20] The way that CAS is performed at our institution universally produces particles measuring 100–500 μm, and with the cerebral microcirculation encompassing vessels with a diameter of <300 μm it is extremely likely that significant cerebral microembolization was prevented.[21] It cannot, however, be excluded that some of the retrieved thrombus/platelet material could have been locally produced inside the EPD. As for the amorphous material, the only feasible source was material dislodged from the target lesion. The importance of calcium was highlighted by the significant differences seen in the composition of particles released from asymptomatic versus symptomatic plaques. This observation and its implications require further exploration.

One can assume that not all of the captured particles, if allowed to embolise to the brain, would have had clinical consequences. Though the aim of some of the previously described studies has been to examine this, the significance of clinically silent embolisation during CEA and CAS is yet to be fully established. Certainly emboli can potentially trigger platelet aggregation and may thus amplify microvascular obstruction[21] and a shower of microemboli could cause similar effects. Furthermore, vasoactive substances contained within plaque or thrombus fragments can cause intense, prolonged vasospasm and subsequent brain infarction.[22]

An interesting finding was noted when the results of pre-operative imaging with CT calcium scores were correlated with the particulate matter captured on a filter-type EPD during CAS: dense/calcified plaques produced greater numbers of small, calcium-rich debris which, as a result of basic scientific experiment, are known to be more injurious to the brain than fibrous emboli.[23,24] This observation may help to explain why the group of patients with asymptomatic plaques in the SAPPHIRE study had worse outcomes than those who were symptomatic; many of such patients underwent CAS without the benefit of an EPD, thereby resulting in greater numbers of small, calcified particles impacting on the brain parenchyma.[4]

As a logical conclusion to this data, it must be suggested that patients with calcified lesions (detected with either duplex or CT) demand the best possible cerebral protection; in such cases a filter-type EPD may not be the most appropriate since it may allow some emboli to pass through its pores, or lead to increased incidence of emboli as measured using transcranial Doppler.[25,26] Flow-reversal or balloon occlusion devices are an alternative, but the potential benefits of emboli reduction must be compared with the potential risks of cerebral malperfusion.

This main finding of greater numbers of calcified particles captured from asymptomatic plaques is in contradiction to a previously published study of electron microscopy of 20 retrieved EPDs.[17] The reasons for the different observation are likely manifold. Malik et al. used a variety of filters and stents during the CAS procedures and used Grey Scale Median (GSM) to assess the plaque structure as opposed to CTA and calcium scoring. A different peri-operative antiplatelet regimen was also employed which may have changed the number of platelet aggregates seen in each study and therefore skewed the results.

Despite the routine use of a filter-type EPD, we maintain that embolisation during CAS (as performed at our institution) is inevitable. Without performing a *post mortem* examination in these cases it is impossible to suggest the size and nature of those emboli that defeat this variety of EPD. Some may argue it is futile to make an analysis of the captured particles when trying to determine their effects, since by their presence in the filter they are asymptomatic emboli. Such data, however, may allow the clinician to extrapolate the peri-operative risks of embolisation for individual cases prior to CAS and thereby provide a personalised treatment (i.e. stent, delivery device, EPD, anticoagulation regimen, open surgery) to reduce these - especially in patients with calcified plaques as determined by pre-operative CT calcium scoring.

5. Conclusion

This study demonstrates that filter-type EPDs collect debris of significant quantity and size during the CAS procedure. Analysis with scanning electron microscopy showed that the collected material is most probably dislocated from the atherosclerotic plaque. Protection devices therefore have the potential to reduce neurological complications caused by emboli measuring greater than the size of the filter pores (typically 100 μm) during the treatment of carotid artery stenosis.

Conflict of interest

Nil declared.

Funding

Mr RE Brightwell's salary and some running costs are paid by a joint Research Fellowship awarded by The Royal College of Surgeons of England and The Stroke Association UK. These sponsors had no role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Ethical approval

Ethical approval for this study was granted by a Local Research Ethics Committee (LREC).

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