Possibilities for reducing procedural embolisation in the endovascular treatment of cervical carotid artery stenosis

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Ph.D. Thesis Booklet

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Introduction

The supraaortic vessels, including the internal carotid artery (ICA) which is one of the main blood supplier of the brain, may be affected by steno-occlusive processes most often atherosclerosis. Embolisation from an atherosclerotic vessel wall or stenosis of critical level may result in transient ischaemic attacks (TIA) or ischaemic stroke. Ischaemia is the predominant cause of stroke, causing some 83% of all stroke events. About 40-50,000 people diagnosed with stroke end up in health care institutions a year in Hungary; stroke accounts for 15% of all mortalities in this country and it is also one of the key causes of death worldwide. In addition to treatments with medicines and surgical interventions, the treatment of ICA stenosis has become an accepted form of treatment. The endovascular treatment of ICA stenosis – carotid artery stenting (CAS) – is, if performed by an experienced and well-prepared interventional neuroradiologist, equivalent from the aspect of complications in patients, to carotid artery endarterectomy (CEA) performed by an experienced surgeon. Recent clinical comparative studies have found practically equal aggregated morbi-mortality rates in the case of CAS and CEA. While in the case of stenting the risk of periprocedural embolisation is higher, in the case of surgery there are higher risks of acute myocardial infarction (AMI), surgery-related infection and complications associated with anaesthesiology. Considering these facts it is obvious that the risks of embolisation of CAS shall be reduced in order to improve success rate of endovascular therapy.

Endovascular catheters and stents used in the treatment of ICA stenosis are variants of devices developed for the haemodynamic reconstruction of peripheral and coronary vessels. Elimination of distal embolisation triggered by the use of catheters was not among the objectives pursued in the development of catheters used in blood flow reconstruction to improve the blood supply of muscle tissues. While in the course of the endovascular treatment of peripheral and coronary artery stenosis a possible embolisation does not result in severe complications thanks to the good collateral network to be found in muscles (resulting from the characteristics of the muscle tissue), in the case of the catheter treatment of an ICA stenosis embolisation resulting from the mechanical manipulation of the plaque-covered vessel may lead to cerebral infarction. Since in the course of the intervention the catheter may come into contact with spontaneously embolising plaques covering the inside of the vessel wall, the force exerted by the catheters and the

resistance of embolising plaques to such physical contact may affect the rate of complications resulting from ICA stenting. Knowledge of the dislodging capability of devices used in the intervention and the plaque resistance to mechanical manipulation playing a role in embolisation may help the interventionist in selecting the therapy that is most suitable for the patient concerned.

Aims

- Study of the catheter manipulation steps required for the endovascular treatment of ICA stenosis in order to establish the degree of embolization using transcranial doppler (TCD) monitoring.
- To study the force exerted by the distal conical tips of various stent delivery systems (SDS) put through the ICA stenosis in order to identify tools with the potentially least embologeneic tips.
- To study different embolic protection devices (EPD) and SDSs pushed through ICA stenosis, from the aspect of the force exerted on plaques covering the vessel wall, on ICA models of various angles of curvature and to analyse forces affecting the vessel wall in arteries with curvatures of different angles in order to determine devices and vessel curvature angles of low embologeneity.
- To study the impacts of the aortic arch (AA) and common carotid artery (CCA) plaques on distal embolisation occurring during CAS by plaque constituents and localisation in order to select patients who are expected to have the lowest embolic complication rate in the course of procedure.

Transcranial Doppler monitoring of distal embolism during carotid stenting

Introduction

In the endovascular treatment of ICA stenosis the various phases of the intervention are carried out using devices of different parameters (including material, diameter, structure /design). The devices of different functions and physical parameters are assumed to entail different risks and likelihoods of embolisation. It is also assumed that real time TCD measurement of the dislodging

of plaques by the different tools in the different phases of the intervention may help the interventionist recognise embolisation caused by catheter manipulation, and improve his/her movements that might potentially most directly contribute to the embolising effect.

Subjects and methods

Intraprocedural TCD examinations were performed between August 2005 and February 2006 during the procedure of stenting ICA stenosis at our institute on a total of 50 patients. No distal embolic protection devices were used, predilation was required in 20% of the cases. In the rest of the cases primary stent implantation was carried out, postdilation was performed in 79.6% of the cases. The ipsilateral a. cerebri media was insonated with a 2 MHz ultrasound head through the temporal window to a depth of 44-58 mm. Emboli were identified on the basis of microembolic signals (MES) in accordance with the relevant international recommendations. Detected microembolic signals were evaluated real-time during the intervention. The endovascular treatment of the ICA was divided into six phases: (1) insertion and entering of the guide catheter, (2) passing the micro-guide wire through the stenosis, (3) predilation, (4) passing the stent delivery system through the stenosis, (5) stent deployment, (6) postdilation.

Results

Embolisation was detected in each patient and – in most cases – in each step. The insertion of the guiding catheter represented the lowest degree of embolisation (2.6 ± 2.9 MES) was observed. The degree of embolization when the .014" micro-guide wire was delivered through the stenosis was proportionate to the time it took to succeed but on the whole it was still modest (3.2 ± 2.3 MES). The most intensive embolisation was observed during predilation (15.9 ± 5.6 MES). The insertion of SDS triggered a 69% higher rate of embolisation than had been observed during the insertion of the micro-guide wire (5.4 ± 2.5 MES). A high rate of microembolic signals was usually observed during the stent deployment (9.2 ± 4.4 MES), similarly to balloon postdilation (10 ± 6.7 MES). A minor stroke was triggered in relation to the periprocedural embolisation in one case. No mortality was recorded within 30 days of the interventions. Micro-embolisation that can always be detected in the course of the endovascular treatment of ICA stenosis remain clinically silent in most cases.

Discussion

In the course of the endovascular treatment of carotid stenosis some degree of microembolisation occurs in practically all cases. Manipulation with guide catheter and micro-guide wire could cause the dislodging of emboli, the number of which grew with the increase of the time spent performing the intervention. The largest amounts of emboli are dislodged in the course of the stenting of the carotid artery the predilation, the stent opening and the postdilation phases. The intensive embolisation upon the opening of the stent and during the balloon postdilation procedure indicates that the stents' mesh structure does not adequately cover the plaques. In the majority of cases the predilation phase and in many cases the postdilation phase may be skipped without jeopardising the success of the intervention. The TCD sound signals immediately informed the interventionist of the embologenity of the ongoing catheter manipulation, apparently prompting him or her to proceed even more cautiously.

Conclusions

The micro-embolisation in the course of the endovascular treatment of ICA stenosis remains clinically asymptomatic in the majority of cases. Higher the intensity of the embolisation higher the risk of damage to the eloquent areas and of the development of subsequent neuro-psychological consequences, therefore the reduction of periprocedural embolisation is important. In the endovascular treatment of ICA stenosis every single step of the catheter manipulation may result embolisation. Three phases with significantly increased MES counts were identified, these were predilation, stent deployment and postdilation. Manipulation with the guide catheter and the micro-guide wire results in the dislodging of increasing numbers of emboli as time passes. The interventionist is immediately informed by the sound signals emitted by the TCD equipment about the embologenity of the ongoing catheter manipulation.

The force transmission of the distal endings of stent delivery systems

Introduction

Among a number of other potential factors the distal ending of the SDS may play a particularly important role in the dislodging of plaques since during interventions – the overwhelming majority of which are carried out without predilation – they may exert considerable force on plaques. The endings of SDSs vary in terms of diameters and the shapes of the tapered tips.

SDSs of diverse sizes and other physical parameters are assumed to have different impacts on the surfaces of plaques, some of which produce even spontaneous embolisation. Our study was aimed at identifying the SDS shape entailing the lowest risk of dislodging emboli.

Subjects and methods

Five different SDSs developed specifically for the endovascular treatment of ICA were studied with a focus on the diameters and shapes of their distal endings. The ratio of the largest diameter of each device to the cross section area of a 5 mm average ICA lumen diameter was calculated, to establish the degree of the stenosis in the case of which mechanical dilatation is always carried out in pushing the device through a stenosis in a straight section of the vessel. Vertical projection (side view) of whose conical tip of which was produced with a digital camera and a Cartesian coordinate system was placed over the pictures. Measurements were taken at 0.05 mm distances along the line of the cone from the distal tip, the ruler and ATAN function of the editing software was used for taking the measurements on the cone tips superimposed over the mm grid paper. The force transmitted by the cone surface has been broken down into forward (causing embolization) and sideways (plaque stabilizing) force vectors. The point where the sideways force exceeded the forward force, that is from which the cone pushes the plaque more sideways, to the vessel wall, than forwards to dislodge it (45º), was identified relative to the distal tip for each tool.

Results

Each of the SDS ends in a tapered cone tip, showing differences in terms of both sizes and arcs.

Device **a** reaches the 45º angle where its diameter is 0.9 mm, it could pass through unblocked through an up to 96.76% stenosis. The cone tip however, meets the shaft in a blunt angle, i.e. the curvature angle increases suddenly to 78.7º at that point, where the diameter of the tool is such that the stenosis may not block more than 89.76% of the vessel lumen. The tip angle of device **b** reaches 45º where its diameter is 0.95 mm, this tool can be put through a stenosis blocking up to 96.39% of the lumen, with a low risk of dislodging emboli. The conical tip and the shaft are joined by a straight tapering section. The angle of tapering of tool **c** reaches 45º where its diameter is 0.7 mm this tool can be put through a stenosis blocking up to 98.04% of the lumen, with a low risk of dislodging emboli. The conical tip and the shaft are joined by a straight

tapering section. The angle of tapering of device **d** reaches 45º where its diameter is 0.8 mm, this tool can be put through a stenosis blocking up to 97.44% of the lumen, with a low risk of dislodging emboli. The conical tip and the shaft are joined by a straight tapering section.

The angle of tapering of device **e** first reaches 45º where its diameter is 0.8 mm. Stenosis up to 97.44% would also be ideal for its insertion however, in the case of this tool the angle of tapering increases to 63.5% where the conical tip meets the shaft owing to the blunt angle in the line of tapering. In the section of transition the angle of tapering returns to 45º where the diameter is 1.48 mm, resulting in a maximum 91.24% stenosis for atraumatic insertion. The conical tip and the shaft are not connected by an evenly tapering section. Devices of a diameter of 5 F do not touch the plaque below a stenosis of a degree as high as 89.2%, therefore from the aspect of this particular study they pose a potential hazard in a smaller percentage of cases. From this perspective devices marked **a**, **c** and **e** appear to be more favourable than those marked **b** and **d** with 6F diameter shaft. Looking at the results of the measurements the device marked **c** was found to have the most atraumatic end design where it has another advantage in that its largest diameter is 5 F.

Discussion

The conical tips of SDSs differ from one another in terms of the forces exerted on the stenotic sections of blood vessels. As the instrument is being pushed forward the force transmitted by the cone surface can be broken down into forward and sideways force vectors, where the sideways force pressing the plaque into the vessel wall and expecting not to cause embolisation, while the forwards force dislodges plaques, causing potentially embolisation. The conical tips of the delivery systems are characterised by the ratio of the difference between the diameters of the cross sections at the two ends of a given section of the cone to the length of the same section, or in other words, the degree to which the cone widens over a given length.

Any unevenness or a step in the cone end surface profoundly affects the directions and strength of force exerted on the vessel wall. Looking at the results of the measurements the device marked **c** was found to have the most atraumatic end design where it has another advantage in that its largest diameter is 5 F, therefore it produces mechanical dilation only in the case of stenosis over 89.2%.

Conclusions

All of the systems tested in our study may always be regarded as safe in terms of the forward pointing dislodging force when being pushed through stenosis not exceeding 89.76%. In the case of occlusions exceeding 89.76% the right choice of the SDSs subject to the devices' conical tip shape may also contribute to minimising periprocedural embolisation. Any unevenness on the catheter surface will result in increased forward pointing (dislodging) forces as a consequence of which the degree of embolisation entailed by the dislodging of plaques may increase. In the development of instruments used in CAS treatments attention must be paid to making sure that there are no edges (steps) in the surface of the tools' conical tips.

Forces exerted on plaques during in vitro measurements by various carotid stent delivery systems and embolic protection devices

Introduction

Carotid stent systems showing major structural differences also differ from one another in terms of their materials and designs. Different EPDs and SDSs are made of different materials, with different material thicknesses and designs, they inevitably feature different pliability characteristics. Depending on the curves in the blood vessel and the pliability of the EPD and SDS a force causing pressure and friction on the vessel wall and consequently the plaque as well, having a negative impact on the stability of the plaque – which might even spontaneously embolise even without such intervention – in accordance with certain simple laws of physics. Our study was aimed at finding the device exerting the smallest force on plaques in the case of vessel morphologies with different curvature angles. We wished to identify the vessel curve angle at which the load on the vessel wall increases significantly during the insertion of an EPD or SDS.

Subjects and methods

Two EPDs and six different SDSs – available on the market, widely used in international practice – were examined. The measurements were carried out with an instrument called IDTE 2000 developed for complex catheter tests, with a CE certificate. A transparent poly-vinyl-clorid (PVC) tube of a 6 mm diameter and a 1.5 mm wall thickness was used as a blood vessel model,

narrowing it to a 5 mm inside diameter at the CCA-ICA bifurcation where an amorphous 12 mm long 75-85% occlusion was created in the lumen. The model was created on the basis of Machine Solution's experiences accumulated in the course of cooperation with catheter manufacturer companies. The insertion range studied using the devices was 12 cm long with a 30 cm/minute rate. The catheters were pushed in automatically by the IDTE 2000 instrument. The tests were carried out on 25º, 50º and 75º angle model settings curved at a distance of 5 cm from the point of entry. A tub filled with 37 ºC tap water was used as medium. Five measurements were taken with each setting, where during the real-time measurements the largest forces exerted by the tool on the vessel wall were recorded in a table.

Results

The SDSs and EPDs tested in our study showed a wide range of differences in terms of the forces exerted on the vessel walls. The intensity of the force exerted by the tools on the vessel wall increased considerably towards higher degree angles. The maximum forces taken in successive measurements on the various tools gradually decreased. The maximum values were always measured during the first trial. The Accunet EPD exerted the weakest force in the case of each angle of curvature, this device was found to be the most atraumatic of all. The strongest force was exerted on the vessel wall in the case of each angle by the Carotid Wallstent SDS.

Discussion

Our measurements showed that SDS and EPD tools exert forces of varying intensity on the vessel wall as they are pushed through narrowed sections. Accordingly, besides a variety of other considerations, this is also very likely to be worth taking into account in selecting the device to be used. The force exerted on the vessel wall is disproportionately higher in tight bends. The EPD resulting load is about a third of the load caused by SDSs however, is an additional contact on plaques in the course of the treatment of the patient, therefore during the endovascular intervention its use entails an additional risk of dislodging of plaques not yet stabilised by stents. Where the narrowed blood vessel section is in a curve of an angle over 50º devices used in the intervention are highly likely to mechanically impact plaques during insertion, alternative treatment option have to be considered. Successive measurements taken by the IDTE system using the same tool indicated significant decreases in the forces exerted by the catheters. This

phenomenon might be explained by the gradual increase of the temperature of the device in the 37 ºC water, therefore the preheating the catheter needs to be under consideration. Another possible explanation might be the expansion of the material as the tool was repeatedly pushed through.

Conclusions

Where CAS instruments need to be inserted in a vessel with bends and curves, the flexibility of the various products should also be taken into account, to minimise the force exerted on the plaque(s). Where the curve in the vessel to be treated with catheter exceeds 50º consideration must be given to other, alternative therapies for the patient, owing to the increase in the load on the vessel wall and the resulting increase in the risk of dislodging emboli. A catheter of room temperature grows softer as it reaches the body temperature, exerting a weaker force on the vessel wall passing through a curve of the same angle. The joint between the distal end of the SDS and the sheath may open up in an excessively tight bend, and it increases the risk of dislodging plaques.

Aortic arch and common carotid artery plaques with soft components pose a substantial risk of cerebral embolisation during carotid stenting

Introduction

Frequent observation that after CAS, fresh ischaemic lesions occur not only in areas supplied by the vessel affected by CAS treatment, but also on the contralateral side and in the posterior fossa. Development of fresh ischaemic lesions in the course of CAS is unlikely to be explained by the presence of ICA plaques only, other embolus sources must also be taken into account. In this study, we examined whether there are relationships between AA and CCA plaques and the development of fresh ischaemic lesions. We also examined whether the composition of plaques affects the degree of embolisation.

Subjects and methods

A total of 101 consecutive cases with symptomatic carotid stenosis were examined retrospectively at our institution. CTA was used to identify the presence or absence of plaques in

the AA and CCA – brachiochephalic artery areas. Two groups were distinguished as plaque analysis: purely calcified and partly or purely soft plaques. Only the vessels that were affected by stenosis were selectively examined with catheter angiography. New ischaemic lesions were detected with diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping. Areas showing restricted diffusion of a high signal on DWI and a low signal on an ADC map were identified as new ischaemic lesions. Depending on localisation, lesions were assigned to three groups: ipsilateral, contralateral, and posterior fossa. The relationships between occurrence of plaques and new ischaemic lesions was analysed with the χ^2 test and Fisher's exact test. Logistic regression models were applied for assessing the effect of risk factors.

Results

New ischaemic lesions were detected in 50% of all cases, only 2% of these DWI lesions were found to be symptomatic. A total of 76% (38/50) of these new lesions occurred in areas that were supplied by vessels affected by treatment (ipsilateral side). A total of 24% of them (12/50) were not related to the treated stenotic lesion (contralateral side and/or posterior fossa). A significant ($p=0.013$) relationship was found between the occurrence of plaques covering the AA and the incidence of new ischaemic lesions. For patients with plaques containing soft components, the increase in risk was 5.617 times compared with plaque-free cases ($p=0.012$). Where the AA plaque was purely calcified, the occurrence of a plaque resulted in a 2.311 times higher risk of embolisation compared with plaque-free cases, but this increase was not significant ($p=0.28$). A significant ($p=0.004$) relationship was found between plaques covering the CCA and the incidence of new lesions. When the CCA plaque contained soft components, the risk of incidence of new ischaemic lesions was 4.411 times higher compared with patients without plaques; ($p=0.006$). If plaques in the CCA were purely calcified, they did not cause any further increase in embolization risk. When patient represented both AA and CCA plaque contained soft components, the risk of incidence of new ischaemic lesions was 7.037 times higher compared with patients without plaques; ($p=0.0003$).

Discussion

In the current study, we found new ischaemic lesions in 50% of all CAS cases that we detected. We found that not all new ischaemic lesions can be regarded as related to the area of the vessel

that has undergone treatment because lesions were also found in 24% of cases on the contralateral side and/or in the posterior fossa. Manoeuvers in the AA during CAS play an important role in the occurrence of new ischaemic lesions in the posterior fossa and contralateral ICA territory. There is a difference between purely calcified plaques and those containing soft components in their potential to produce emboli. Therefore, composition of plaques can be a factor involved in cases of plaques in the AA and CCA. In cases where no plaques were present in the AA, we did not encounter any new lesions outside the territory supplied by the vessel in question. This lack of finding confirms our notion of new contralateral and posterior fossa ischaemic lesions originating in the AA. We found a relationship between the presence of AA and CCA plaques contains soft component and the development of fresh ischaemic lesions. These results suggest that plaques with soft components in the AA and CCA increase the risk of periprocedural embolisation. The AA and CCA form part of the intervention route that is used in the course of ICA stenting where the guide wires and catheters come into contact with and mechanically insult the vessel walls with plaques on them. Therefore, both of these areas are assumed to increase the rate of complications of embolisation in CAS.

Conclusions

In the case of an AA or CCA without plaques or with homogeneous calcified plaques CAS is a form of treatment entailing low risk of embolisation. The presence of soft plaque components in the AA or the CCA results in a significantly higher risk of CAS embolisation in comparison to AA and CCA cases without plaque. In the examination of patients with ICA stenosis mapping the AA and CCA areas using CTA may be highly useful in clarifying the risks of endovascular treatment. Before the application any embolic protection requires incision on CCA or balloon dilatation in CCA an examination of the presence of plaques in the CCA is highly recommended.

New findings

- In the endovascular treatment of ICA stenosis every single step of the catheter manipulation (insertion of the guide wire; insertion of the guide catheter; predilation, SDS delivery through the stenosis, stent deployment, balloon dilation) may result in embolisation.

- The interventionist is immediately informed by the sound signals emitted by the TCD equipment about the embologeneity of the ongoing catheter manipulation.
- The conical tips of stent delivery systems differ from one another in terms of the forces exerted on the narrowed sections of blood vessels.
- All of the stent delivery systems tested in our study may always be regarded as safe in terms of the forward pointing dislodging force when being pushed through stenoses not exceeding 89.76%.
- Any edge forming will result in an increase dislodging forces, entailing an increased risk of embolisation when the device comes into contact with the plaque.
- The different stent delivery systems exert forces of different intensities on the vessel walls while passing through the narrowed vessel section.
- The force exerted on the vessel wall increases not proportionally but significantly more than the increase in the angle of the curve in the blood vessel.
- EPDs exert pressure on the vessel wall while being pushed through the angled vessel stenosis, but its intensity is smaller than the force exerted by SDSs.
- Over angles of curvature exceeding 50º consideration must be given to other, alternative therapies for the patient, owing to the increase in the load on the vessel wall (plaque) and the resulting increase in the risk of dislodging emboli.
- A catheter of room temperature grows softer as it reaches the body temperature, exerting a weaker force on the vessel wall passing through a curve of the same angle.
- The joint between the distal end of the SDS and the sheath of the stent may open up in an excessively tight bend, and the edge entails a risk of dislodging plaques.
- In the examination of patients with ICA stenosis mapping the AA and CCA areas using CTA may be highly useful in clarifying the risks of endovascular treatment.
- Before the application any kind of POD examination of the presence of plaques in the CCA is highly recommended.

Practical benefits of the findings

At present there are two invasive solutions for the treatment of neck carotid artery stenosis that may be regarded as more or less equivalent: CEA and CAS. The most significant disadvantage of the CAS – which is otherwise less stressful for the patient – relative to the CEA is its higher risk of embolisation.

The main practical benefit of our work is that our results enable mitigating the embolisation risk of CAS in three different aspects:

As was proven by TCD tests a certain amount of emboli are found to be dislodged in each procedural step of CAS. One obvious solution is therefore the skipping of steps that are not vitally important, such as predilation and in some cases also postdilation. Intraprocedural TCD monitoring may also be useful by emitting sound signals to the interventionists warning him or her of the density of emboli, calling for more cautious manipulation. This may be particularly important during the earlier stages of the learning curve.

The tools available on the market have a variety of advantages and disadvantages in comparison to each other in terms of potential embolisation. Efforts must therefore be made to use the most atraumatic devices. The risk of dislodging plaques can be mitigated by using stent delivery systems with the smallest possible diameters and by choosing tools with smooth elongated conical tips without any edges. The force exerted by the delivery system on plaques in bends in the vessel may be reduced by increasing the pliability of the delivery system. According to our results where the narrowed blood vessel section is in a curve of an angle over 50º the tools used in the intervention are highly likely to mechanically impact plaques during insertion. The plaque stabilising capability of the implant is also crucial; from the aspect of periprocedural embolisation covered stents are a safer choice than metal mesh stents. In the development of the CAS tool kit attention must be paid to improving the physical attributes of relevance to periprocedural embolisation.

Various randomised studies naturally fail to deal with the mitigation of embolisation by choosing suitable patients. In our view this may be highly important in avoiding complications. CTA provides information not only on the position of plaques on the vessel wall but also their structural components, and consequently their embologeneity. In addition to the examination of neck's carotid stenosis this technique is also suitable for examining the AA and CCA at the same time, showing the positions and quantity of potentially embologeneic plaques.

Knowledge of the physical attributes of CAS devices – in view of the embologeneity of the ICA, AA and CCA they need to pass through – may contribute to reducing periprocedural complications in the case of the endovascular treatment of ICA stenosis. With this information in mind it is possible to decide which intervention entails lower risks for the patient.

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