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Computed tomography indicators of cerebral microperfusion improve long term after carotid stenting in symptomatic patients

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Objectives: We tested the hypothesis that computed tomography (CT) perfusion markers of cerebral microcirculation would improve 36 months after internal carotid artery stenting for symptomatic carotid stenosis while results obtained 6–8 weeks after the stenting procedure would yield a predictive value. Methods: We recruited consecutive eligible patients with >70% symptomatic carotid stenosis with a complete circle of Willis and normal vertebral arteries to the observational cohort study. We detected changes in the cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), time to peak (TTP) and permeability surface area-product (PS) before and after carotid stenting. We have also compared the absolute differences in the ipsilateral and contralateral CT perfusion markers before and after stenting. The search for regression models of "36 months after stenting" results was based on a stepwise analysis with bidirectional elimination method. Results: A total of 34 patients completed the 36 months follow-up (15 females, mean age of 69.68±S.D. 7.61 years). At 36 months after stenting, the absolute values for CT perfusion markers had improved: CBF (ipsilateral: +7.76%, contralateral: +0.95%); CBV (ipsilateral: +5.13%, contralateral: +3.00%); MTT (ipsilateral: –12.90%; contralateral: –5.63%); TTP (ipsilateral: –2.10%, contralateral: –4.73%) and PS (ipsilateral: –35.21%, contralateral: –35.45%). MTT assessed 6–8 weeks after stenting predicted the MTT value 36 months after stenting (ipsilateral: R2=0.867, contralateral R2=0.688). Conclusions: We have demonstrated improvements in CT perfusion markers of cerebral microcirculation health that persist for at least 3 years after carotid artery stenting in symptomatic patients. MTT assessed 6–8 weeks after stenting yields a predictive value.

Key words: carotid artery stenosis, mean transit time, permeability surface area-product, cerebral blood flow, computed tomography perfusion

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Abbreviations: BBB, blood brain barrier; CTP, computed tomography perfusion; CBV, cerebral blood volume; CBF, cerebral blood flow; DSA, digital subtractive angiography; MTT, mean transit time; NECT, non-enhanced CT; NASCET, North American Symptomatic Carotid Endarterectomy Trial; ROIs, Region of Interest; RICA, Right internal carotid artery; PS, permeability surface area-product; TIA, Transient ischemic Attacks; TTP, time to peak

INTRODUCTION

It has been recently postulated that it is not just the degree of internal carotid artery stenosis that adversely influences the cognitive aging but rather that the vascular stiffening provides a potential target for ameliorating the age-related cognitive decline. Consequently, augmented pulse pressure or carotid pulsatility were suggested to be more important in the development of white matter hyperintensities and declining cognitive function than the carotid artery stenosis itself (Aribisala *et al.*, 2014; Singer *et al.*, 2014; van Sloten *et al.*, 2015; Wardlaw *et al.*, 2017).

We have recently described a complex picture of a regional resting state perfusion variability in subjects with chronic carotid artery stenosis before the stenting procedure (Szarmach *et al.*, 2018). Our study had shown a relatively well-balanced circulation, as measured by uniform regional response to an acetazolamide test, with low or very low cerebral blood flow (CBF) in these subjects (Szarmach *et al.*, 2018). All of these findings taken together suggest that subjects with carotid artery stenosis represent a state of chronic cerebral hypoperfusion.

Animal models of chronic brain hypoperfusion, in turn, provide evidence that a decrease in the blood supply is associated with complex pathophysiological changes encompassing hypoxia, inflammation and oxidative stress (Kim *et al.*, 2012; Duncombe *et al.*, 2017). Furthermore, long-term hypoperfusion potentially accelerates the development of age-related ultrastructural aberrations of capillaries resulting in disruption of the blood brain barrier (BBB). BBB damage, in turn, is considered as a main initial pathogenic mechanism in the cerebral small vessel disease (Ding *et al.*, 2017).

It becomes clear that improvement in outcomes for patients with carotid stenosis requires a better understanding of chronic changes in the brain macro and microcirculation. It can be crucial for better use of such procedures as carotid endarterectomy or stenting. Furthermore, it may open new perspectives in terms of such medical interventions as encouraging healthy life-

style habits and appropriate use of medication (Abbott, 2016). Consequently, when assessing effects of the carotid stenting, a wider perspective should be taken into account. In particular, apart from the well-recognised beneficial effect of atherosclerotic plaque stabilisation and widely studied CBF, other less recognized radiological markers encompassing the brain microcirculation and inflammatory status should be analysed. Furthermore, long term effects of carotid artery stenting are poorly understood. Computed tomography perfusion (CTP) provides an easy and fast way of obtaining colour-coded maps quantifying such perfusion parameters as CBF, cerebral blood volume (CBV), mean transit time (MTT), time to peak (TTP) and permeability surface area-product (PS).

CTP gives an opportunity to measure physiological parameters of microcirculation in the brain by fast acquisition of bolus injection of the contrast agent. CBF is expressed in millilitre per 100 g wet weight of the brain tissue per minute (ml/100 g/min). This parameter provides information on the quantity of blood flowing across a particular region of the brain. CBV is calculated in millilitre per 100 g wet weight of the brain tissue (ml/100 g). This provides information on the amount of blood remaining in the microcirculation. MTT reflects the time difference between the arterial inflow and the venous outflow. It is expressed in seconds (sec.). TTP reflects the time elapsing until the maximum concentration of contrast agent is reached within the ROI (sec.). PS measures the permeability of the BBB to contrast material (expressed in ml/min/100ml tissue) (Cuenod & Balvay, 2013). In healthy subjects, the intact BBB is impermeable for large molecules, such as the iodinated contrast agent. In neoplasms, inflammatory/infectious states, ischaemia, and neurodegenerative diseases, the BBB is impaired, and the diffusion of fluid, blood or contrast molecules into the extravascular space is augmented (Jain *et al.*, 2008; Topakian *et al.*, 2010; Avsenik *et al.*, 2015). PS was higher in the investigated sample when compared to the control subjects, indicating BBB impairment and enhanced permeability (Szarmach *et al.*, 2017).

It is particularly tempting to use the combination of MTT and PS to assess the brain pathophysiology before and after carotid artery stenting. MTT, defined as the average transit time of blood through a given brain region (measured in seconds), seems particularly sensitive to changes in the brain perfusion characteristics (Waaijer *et al.*, 2007). PS, in turn, may provide a radiological marker of inflammatory states, ischaemia and neurodegenerative processes that typically compromise the BBB (Topakian *et al.*, 2010; Taheri *et al.*, 2011; Yang *et al.*, 2011; Yang *et al.*, 2015). In addition, BBB and PS taken together may be potentially considered as radiological markers of the cerebral small vessel disease (Cao *et al.*, 2016; Arba *et al.*, 2017). Consequently, we hypothesised that MTT and PS may provide useful predictive information with respect to the internal carotid artery stenting results 36 months post stenting procedure in patients with chronic carotid artery stenosis.

MATERIALS AND METHODS

Patient sample. Test power analysis was used prospectively to estimate the study sample size. Our own observations suggested values of mean and SD before stenting. A sample size consisting of 34 was based on calculations for those CT parameters assuming $\alpha=0.05$ and $1-\beta=0.9$.

The following inclusion criteria were defined:

1. Age>18 years.
2. Written consent to participate in the study.
3. Symptomatic stenosis of more than 70% within a single internal carotid artery (without vertebral and subclavian flow disturbances) were included in the study.
4. Complete circle of Willis and normal vertebral arteries confirmed by digital subtractive angiography (DSA).

Symptomatic carotid disease was defined as focal neurologic symptoms that were sudden in onset and referable to the appropriate carotid artery distribution (ipsilateral to significant carotid atherosclerotic pathology), including one or more transient ischemic attacks (TIA) or one or more minor (non-disabling) ischaemic strokes (IS; NASCET, 1991). The definition is contingent on the occurrence of carotid symptoms within the 6 previous months (NASCET, 1991; MRC, 1991). Diagnosis of IS was based on the WHO's definition: "clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin". Hemorrhagic stroke was excluded by brain CT. If duration of symptoms was <24 hours, TIA was diagnosed (WHO Monica Project, 1988).

Degree of stenosis was diagnosed on the basis of a Doppler examination according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET, 1991) criteria and was confirmed by DSA directly before the stent implantation. Carotid duplex ultrasound was at a clinical follow-up visits 1 month after treatment, 6 months and then annually after enrolment.

The following exclusion criteria were specified:

1. Significant (>70%) tandem carotid stenosis.
2. Intracranial tumours, aneurysm, vessel malformations.
3. Post-stroke disability (modified Rankin score (mRs) >1), cognitive impairment (Mini-Mental State Examination <24 or The Lawton Instrumental Activities of Daily Living Scale <3).
4. Uncontrolled hyperthyroidism.
5. Hypersensitivity to iodine or history of adverse effects following the administration of contrast agents.
6. Stage II–V renal insufficiency were excluded from the study.

Between April 2010 and December 2014, initially a total of 107 patients were subjected to internal carotid artery stenting procedures at the Department of Cardiac and Vascular Surgery of the Medical University of Gdansk. 55 patients fulfilled the enrolment criteria. Consecutive eligible patients were recruited. Eight subjects did not agree to a control examination after 36 months, eight subjects had died and four subjects had changed their place of living. Finally, 34 subjects accomplished the study, (15 females (44.1%) and 19 males (55.9%); mean age of 69.68±standard deviation (SD) 7.61 years). Risk factors and concomitant diseases in the studied sample are provided in Table 1. We do not have detailed information regarding the medical treatments received by patients.

This study was carried out in accordance with the recommendations of the Declaration of Helsinki, with written informed consent from all subjects. The protocol was approved by the Independent Ethics Committee of the Medical University of Gdansk (NKBBN/383/2008).

Imaging protocol. To evaluate the cerebral blood supply in all subject patients, three CTP examinations were carried out: the first was performed 24 hours before the internal carotid artery stenting procedure, the second was performed 6–8 weeks afterwards, while the

Table 1. Risk factors and concomitant diseases in the studied sample.

Risk factors and concomitant diseases	N (%)
Total number of patients	34
Age	69.68 ± SD 7.61
Women	15 (44.1%)
Active smokers	12 (35.3)
Arterial hypertension*	28 (82.4)
Diabetes mellitus type 2**	10 (29.4)
COPD****	3 (8.8)
Transient ischemic attack (TIA)	29 (85.3)
Ischemic stroke (IS)	5 (14.7)
Coronary artery disease****	22 (64.7)
Lipid disorders***	10 (29.4)
Myocardial infarction****	12 (35.3)
Chronic kidney disease****	1 (2.9)

COPD, chronic obstructive pulmonary disease; SD, standard deviation; IS and TIA, according to WHO definitions (WHO Monica Project, 1988); *history and antihypertensive treatment; **history or hypoglycemic treatment; ***history or lipid lowering treatment; ****confirmed by hospital or out-patient documentation

third was 36 months (±4 months) post stent implantation.

Our CT perfusion technique has been previously described in detail (Szarmach *et al.*, 2016; Szarmach *et al.*, 2017; Szarmach *et al.*, 2018). Briefly, all CT examinations were performed with the use of the same scanner (64-MDct Light Speed VCT XT, GE Healthcare Technologies, Wisconsin, USA).

The CT protocol consisted of non-enhanced CT (NECT) images that were obtained with such parameters as: 5-mm contiguous axial sections from vertex to skull base, tube voltage and current=140 kVp, 335 mAs, 0.9 second rotation time, the number of images=56, total exposure time=6.3 s, and CDTIvol between 50 and 60 mGy.

CTP studies were acquired during injection of 40 ml of the contrast agent (Optiray 350 Mallinckrodt, St. Louis, Missouri, USA) with a flow rate of 4 ml/s followed by 40 ml saline using an antecubital intravenous injection.

Perfusion imaging was obtained at eight levels (40 mm thick axial scans) with the following parameters: tube voltage=80 kVp, current=150 mAs, slice thickness=5 mm, rotation time=1/s, number of images per rotation=8, cine time between images=0.5 s, image matrix=512×512, field-of-view (FOV)=25 cm, time interval between reconstructed images=0.5 s and interval=0 mm. A total of 360 slices were obtained with a total scan time of 45 seconds. CDTIvol was approximately 390 mGy per examination.

The first scan was set at the basal ganglia, above the level of the circle of Willis.

The arterial input function was chosen within the anterior cerebral artery. The venous output region was selected from the superior sagittal sinus.

Image post-processing. CT perfusion data were transferred to a post-processing workstation (AW 4 GE Healthcare Technologies, Wisconsin, USA) with a professional software package (CT Perfusion version 4 (v 4.3.1), GE Healthcare Technologies, Wisconsin, USA) to create colour maps of CBV, CBF, MTT, TTP and PS.

All subjects were analysed using the same equipment and post-processing software, increasing the reliability of the obtained results.

Two, 10-year experienced neuroradiologists (blinded to side and time of operation) independently drew two standardised elliptical mirrored regions of interest (ROIs) manually. Each ROI (approximately 20 cm² each) was determined at all of the analysed levels (Fig. 1a, b), over

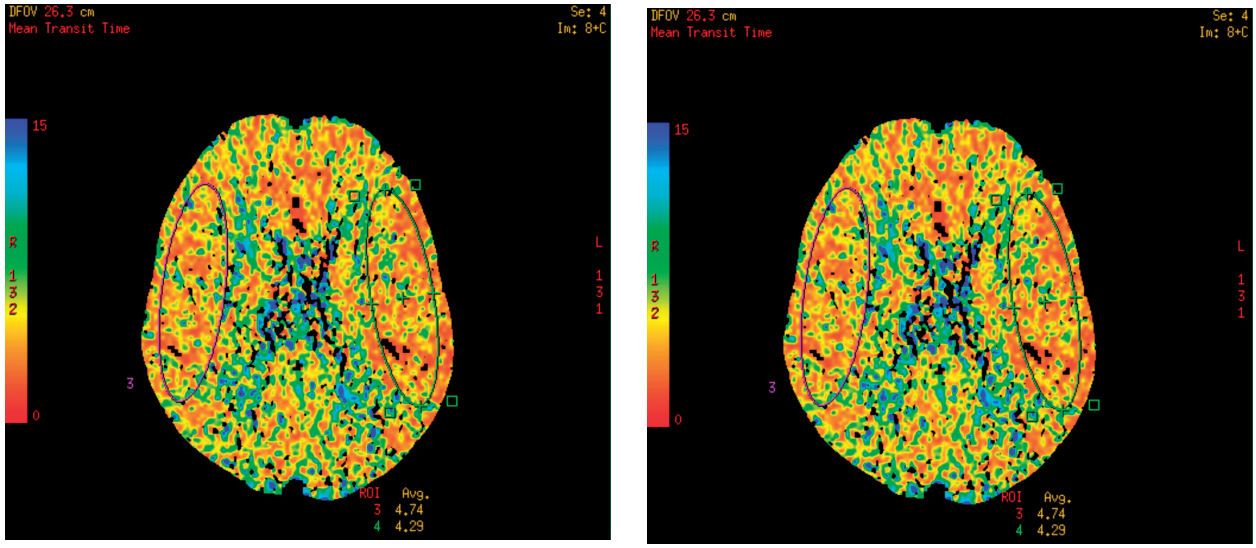

Figure 1. Mean Transit Time (MTT) CTP images in a patient with severe right internal carotid artery (RICA) stenosis.
Regions of interest (ROIs) placed on MCA (Middle Cerebral Artery) territories. Before (left) and 3 years after (right) carotid artery stenting. Decline in the average MTT after stenting was visible in both hemispheres. Colour scale corresponds to the different MTT values (blue, elongate; red, shortened).

Table 2. Comparison of CTP values before stenting and 36 months post stenting.

Variable	Parametric t Tests for dependent samples Number of observation = 34 CT_3, CTP parameter long after stenting; CT_1, CTP parameter before stenting				
	Side	Mean ±SD (Median)	Change	T	P
MTT_1	Ipsilateral	4.667±1.381 (4.181)	−12.90%	4.046	<0.001
MTT_3		4.065±0.855 (3.825)			
MTT_1	Contralateral	4.313±0.875 (4.104)	−5.63%	2.456	0.019
MTT_3		4.070±0.702 (3.979)			
CBV_1	Ipsilateral	1.735±0.288 (1.739)	+5.13%	−1.604	0.118
CBV_3		1.824±0.323 (1.823)			
CBV_1	Contralateral	1.769±0.307 (1.706)	+3.00%	−0.876	0.388
CBV_3		1.822±0.283 (1.810)			
CBF_1	Ipsilateral	37.412±9.129 (37.866)	+7.76%	−2.341	0.025
CBF_3		40.315±7.822 (42.102)			
CBF_1	Contralateral	39.002±6.630 (38.178)	+0.95%	−0.295	0.770
CBF_3		39.374±5.148 (39.238)			
TTP_1	Ipsilateral	25.762±3.275 (25.539)	−2.10%	0.537	0.595
TTP_3		25.220±7.025 (24.577)			
TTP_1	Contralateral	25.527±3.257 (25.199)	−4.73%	4.246	<0.001
TTP_3		24.319±3.419 (24.611)			
PS_1	Ipsilateral	1.542±0.795 (1.369)	−35.21%	4.462	<0.001
PS_3		0.999±0.268 (1.030)			
PS_1	Contralateral	1.478±0.781 (1.378)	−35.45%	4.007	<0.001
PS_3		0.951±0.320 (0.943)			
$rMTT_1$	---	1.094±0.273 (1.060)	−7.59%	1.439	0.155
$rMTT_3$		1.011±0.195 (0.988)			
$rCBV_1$	---	0.961±0.192 (0.962)	+6.56%	−1.520	0.134
$rCBV_3$		1.024±0.150 (1.017)			
$rCBF_1$	---	0.990±0.088 (1.006)	+1.11%	−0.581	0.563
$rCBF_3$		1.001±0.067 (1.001)			
$rTTP_1$	---	1.010±0.029 (1.006)	+2.08%	−0.658	0.515
$rTTP_3$		1.031±0.189 (0.997)			
rPS_1	---	1.087±0.335 (1.057)	+0.74%	−0.120	0.905
rPS_3		1.095±0.239 (1.061)			

the cortical grey matter centred 20 mm from the margin of the brain. The large vessels and bones were automatically excluded *via* the brain perfusion software.

Our perfusion application offers two different models of evaluation: the "neuro brain stroke" and the "neuro brain tumour". The first mode applies the maximal slope method (Fiorella *et al.*, 2004; Szarmach *et al.*, 2016; Szarmach *et al.*, 2017) for measurement of CBF, CBV, MTT or TTP, while the second one calculates microvascular permeability (PS) and the fractional blood volume based on the Johnson and Wilson model (St Lawrence & Lee, 1998a; St Lawrence & Lee, 1998b).

The absolute values of CT perfusion parameters (CBF, CBV, MTT, TTP, and PS) of one hemisphere in the region of the middle cerebral artery distribution and contralateral mirroring areas in functional maps were calculated.

Statistical analysis. To compare results before and after stenting, differences in the absolute CTP values (CBF, CBV, MTT, TTP and PS) and side to side relative values (rCBF, rCBV, rMTT, rTTP, rPS-obtained as the ratio of appropriate values from ipsilateral side to contralateral side to stenosis) were analysed.

All raw data were presented with their descriptive statistics, such as the number, mean, SD and percentage change. Materials were collected from all individual slices, measured by two independent specialists and finally averaged per patient. Differences between the mean values were examined by parametric Welch's t-test (symbol t).

The search for regression models of "36 months after stenting" results were based on a stepwise analysis with bidirectional elimination method. The set of possible explanatory variables were: "before stenting", "just after stenting" outcomes and also the degree of stenosis information (70–89%, low; 90–99%, high). The level of significance was set at α=0.05. All calculated p-values

Table 3. Results of linear one-dimensional regression models for CTP parameters.

CT_3	Linear regression model for CTP parameters $CT_3 = a_1 + a_1 \times CT_2$; CT_3, CTP parameter 36 months after stenting; CT_2, CTP parameter 6-8 weeks after stenting							
	Side	Model				F (*p*-value)	SE	R^2
		Coefficients		Error	t (*p*-value)			
MTT_3	Ipsilateral	a_1	1.100	0.209	5.265 (<0.001)	215.39 (<0.001)	0.312	0.867
		a_2	0.752	0.051	14.676 (<0.001)			
	Contralateral	a_1	1.265	0.334	3.792 (0.001)	73.69 (<0.001)	0.392	0.688
		a_2	0.752	0.088	8.584 (<0.001)			
CBV_3	Ipsilateral	a_1	0.629	0.241	2.611 (0.014)	25.42 (<0.001)	0.245	0.425
		a_2	0.588	0.117	5.042 (<0.001)			
	Contralateral	a_1	0.785	0.225	3.492 (0.001)	21.92 (<0.001)	0.221	0.388
		a_2	0.512	0.109	4.681 (<0.001)			
CBF_3	Ipsilateral	a_1	11.426	3.833	2.981 (0.005)	59.42 (<0.001)	4.700	0.639
		a_2	0.639	0.083	7.708 (<0.001)			
	Contralateral	a_1	22.920	3.447	6.649 (<0.001)	23.71 (<0.001)	3.962	0.408
		a_2	0.353	0.072	4.869 (<0.001)			
TTP_3	Ipsilateral	a_1	–8.051	7.260	–1.109 (0.276)	21.37 (<0.001)	5.524	0.382
		a_2	1.405	0.304	4.622 (<0.001)			
	Contralateral	a_1	0.972	1.864	0.521 (0.606)	159.53 (<0.001)	1.419	0.828
		a_2	0.994	0.079	12.630 (<0.001)			
PS_3	Ipsilateral	a_1	0.580	0.111	5.224 (<0.001)	16.11 (<0.001)	0.222	0.314
		a_2	0.512	0.128	4.013 (<0.001)			
	Contralateral	a_1	0.426	0.119	3.589 (0.001)	22.49 (<0.001)	0.249	0.394
		a_2	0.652	0.137	4.742 (<0.001)			

were for two-tailed tests. Full model description is provided in the Supplement. All raw data were analysed using the statistical software Statistica 13.1 (StatSoft, Tulsa, OK, USA).

RESULTS

Absolute CBF (ipsilateral: +7.76%, contralateral: +0.95%); CBV (ipsilateral: +5.13%, contralateral: +3.00%); MTT (ipsilateral: –12.90%; contralateral: –5.63%); TTP (ipsilateral: –2.10%, contralateral: –4.73%) and PS (ipsilateral: –35.21%, contralateral: –35.45%) values had improved 36 months after carotid artery stenting (Table 2). We did not observe significant changes in the side to side relative values of the reported CT parameters (Table 2).

Comparison of CTP values before stenting and 6-8 weeks after stenting has been already published (Szarmach *et al.*, 2014). The results are provided as Supplemental Table 1 at www.actabp.pl.

MTT and PS outcomes 6–8 weeks after stenting (Table 3) predicted MTT and PS results 36 months after stenting for both, the ipsilateral and contralateral side. The higher the R^2 value is, the stronger is the predictive value. The best prognostic value (in terms of coefficient R^2 determination) had the models for MTT parameters: R^2=0.867 and R^2=0.688 for the ipsilateral and contralateral side, respectively (Fig. 2 and Fig. 3). Consequently, in the case of MTT parameters and for both hemispheres, we may expect that the higher the values after stenting, the higher the values over time. To be precise, a unit higher just after stenting, results in a 0.75 increment in the long term. In another words, in the next 4 years after stenting, MTT is losing about 25% of its increase. PS outcomes 6–8 weeks after stenting yielded weaker prognostic value than MTT, with R^2=0.314 for ipsilateral side and R^2=0.394 for contralateral side (Table 3). Other CTP parameters (CBF, CBV, TTP) did not provide any prognostic values.

At 36 months, two patients (5.9%) who underwent the carotid artery stenting had restenosis. The degree

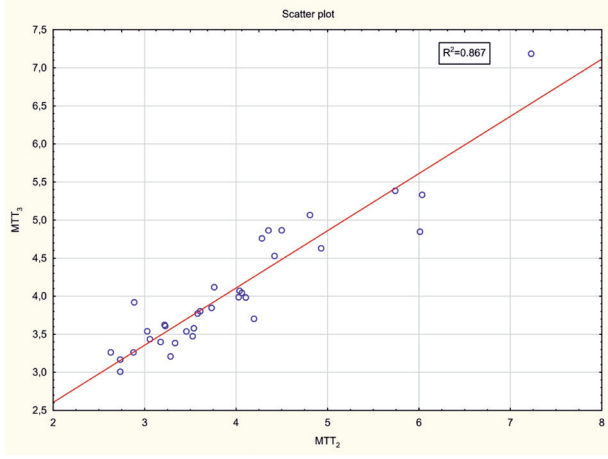

Figure 2. Scatter plot of MTT 36 months after stenting (MTT_3) *vs.* just after stenting for the ipsilateral side (MTT_2).

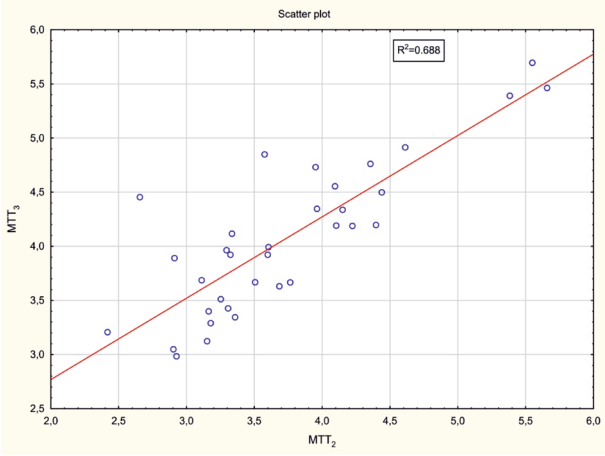

Figure 3. Scatter plot of MTT 36 months after stenting (MTT_3) *vs.* just after stenting for the contralateral side (MTT_2).

of stenosis immediately after 34 stents was below 15% and in the two patients with restenosis, the stenosis at 36 months had progressed to 60–69% and 70–79%, respectively (Supplemental Table 2 and 3 at www.actabp.pl). In the remaining patients, stenosis was below 50%. None of the patients had a stroke, myocardial infarction or died within 30 days of carotid stenting. None of the investigated patients had a stroke, TIA or myocardial infarction during 36 months post stenting.

DISCUSSION

There are two main findings of the study presented here: 1) CBF, CBV, MTT, TTP and PS improve 36 months after carotid artery stenting, 2) MTT and PS assessed 6–8 weeks after stenting predict the MTT and PS values 36 months post stenting.

Strong interdependence between severity of microcirculation impairment and the time-based perfusion parameters has been recently reported. In particular, MTT appears to show a good association with the cerebral small vessel disease (Cao *et al.*, 2016; Arba *et al.*, 2017). There is actually a good pathophysiological reasoning explaining such interdependence. Leukoaraiosis, the radiological marker of cerebral small vessel disease, is linked to arteriolar tortuosity and thickening of the walls of periventricular veins and venules (Brown *et al.*, 2002). Such changes in the shape and elastic properties of small vessels are very likely to affect the blood flow and, in turn, the average transit time of blood through an affected brain region. Moreover, chronic hypoxia and prolonged inflammatory status evoke the platelet activation and increase the pro-coagulative status (Oberheiden *et al.*, 2010), which may further slowdown the blood flow velocity.

Our study demonstrates for the first time the predictive role of MTT in subjects undergoing carotid artery stenosis stenting. Consequently, lack of improvement in the MTT parameter shortly after stenting procedure may potentially indicate a higher risk of developing the ischemic stroke or cognitive deterioration. Further studies are needed to establish a link between improvement in a radiological surrogate marker, such as MTT, and functional benefits for patients.

BBB impairment is another typical feature of the small vessel disease (Hassan *et al.*, 2003; Wardlaw *et al.*, 2009). Obviously, BBB dysfunction provides a pathophysiological substrate for improper neurovascular unit activity and general dysregulation of microcirculatory responses to changes in the metabolic demand of neurons (Hassan *et al.*, 2003). Consequently, carotid artery stenting effects are not only limited to CBF improvement but also encompassed in a wide range of modifications to the ischaemic status of the brain. This study confirms our earlier results demonstrating that the carotid artery stenting and subsequent reperfusion diminish the BBB permeability (Szarmach *et al.*, 2017). In addition, we show that it has a long term effect.

Quite surprisingly, PS, the radiological marker of BBB permeability, provided a weaker predictive value than MTT. BBB impairment is a multifactorial process consisting of several pathomechanisms, which actually may decrease its predictive value. Alternatively, the total scan time used in our study was 45 s, while typically for measurement of PS, a longer acquisition time is recommended to avoid overestimation. For the first-pass CTP data, it is advised to obtain acquisition for at least 90 s and combine it with delay correction for 90 s CTP acquisition. The data available for the Patlak model suggest that shorter acquisitions may result in BBB permeability overestimation (Dankbaar *et al.*, 2008; Hom *et al.*, 2009). Consequently, the reported PS values may be overestimated. However, even if the BBB values are overestimated, the same procedure was adopted before and after stenting. Therefore, the relative changes remain valid.

Several authors had reported CBF and MTT improvements in the early postinterventional phase (ranging from one day to a few weeks) after either carotid endarterectomy or stenting (Niesen *et al.*, 2004; Gaudiello *et al.*, 2008; Tavares *et al.*, 2010; Ding *et al.*, 2016; Szarmach *et al.*, 2017). In turn, CBV assessed shortly (from one day to a few weeks) after the mentioned procedures either did not change (Matsubara *et al.*, 2009; Tavares *et al.*, 2010) or had increased (Kawai *et al.*, 2014; Piñero *et al.*, 2014; Ding *et al.*, 2016; Szarmach *et al.*, 2017). Only Trojanowska and others (Trojanowska *et al.,* 2006) reported the perfusion parameter improvement in both hemispheres (CBF increase, MTT and CBV decline) that persisted 6 months after carotid artery stenting. To the best of our knowledge, our study provides for the first time evidence that the beneficial effect is much longer and may last over 3 years. Quite interestingly, CBF long-term beneficial effect is limited to the ipsilateral side of stenting. CBV is not affected in both hemispheres. Thus, the MTT and PS decline that is visible in both, ipsilateral and contralateral sides, may suggest that stenosis present at the ipsilateral side before the carotid artery stenting affected both brain hemispheres, in terms of microcirculatory and inflammatory impairment. Consequently, by combining MTT and PS, we were able to propose that carotid artery stenting may have a profound effect on the time course of cerebral small vessel disease in both hemispheres.

Several authors suggest that relative perfusion parameters (the symptomatic hemisphere-to-asymptomatic hemisphere CBF, CBV and MTT ratios) may represent an early and sensitive parameter for the detection of perfusion changes (Wilkinson *et al.*, 2003; Duan *et al.*, 2012; Merckel *et al.*, 2012). In the Wilkinson and others (Wilkinson *et al.,* 2003) and Duan and others (Duan *et al.,* 2012) studies, the relative CBF had increased and MTT had diminished, while the relative CBV did not change immediately (one day) after revascularisation. In the Merckel and others (Merckel *et al.,* 2012) study, the

relative CBF and CBV had augmented, while MTT had declined one day after procedure. In our study, we did not observe changes in the relative CBF, CBV, MTT, TTP and PS. Our study sample consisted of patients with complete circle of Willis and normal vertebral arteries, while the CBF and CBV before stenting were low, suggesting a relatively well balanced collateral circulation (Szarmach *et al.*, 2017). Consequently, stenting at the ipsilateral side limited the need for collateral supply, also improving circulation in the contralateral hemisphere. Taken together, it is not surprising that our relative CBF, CBV, MTT, TTP and PS indices did not change.

In-stent restenosis occurs more frequently, and the risks for ipsilateral ischaemic stroke and brain microinfarcts are higher after stenting than after endarterectomy (Bonati *et al.*, 2009; Arquizan *et al.*, 2011; Lal *et al.*, 2012). Nevertheless, in the 2010–2014 years, when the study was conducted, internal carotid artery stenting was a frequently used procedure at our university hospital. CTP and Doppler ultrasound were a standard method of choice for perfusion and stenosis assessment in these patients. Therefore, frequency of microbleeds, micro ischemic strokes and functional status were not assessed. Such assessments, with the use of diffusion weighted (DWI) and blood-oxygenation level-dependent (BOLD) magnetic resonance imaging are currently under way. Actually, the aim of this study was not to compare carotid stenting versus endarterectomy, but to demonstrate that reperfusion benefits are not limited to CBF, and also encompass improvement in microcirculation and BBB integrity. In our study sample, two subjects suffered from restenosis (5.9%) during 36 months post stenting. Thus, the percentage was slightly lower when compared to restenosis frequency reported by other authors (Arquizan *et al.*, 2011; Lal *et al.*, 2012).

The main disadvantage of CTP is related to concerns associated with a high radiation dose. In our study, conventional angiography was anyway used to confirm the degree of stenosis. There are several advantages of CTP, like an easy and fast way acquisition of perfusion-related parameters and a wide availability. In terms of MTT, CTP provides comparable data with magnetic resonance imaging (MRI). Ultra-low-dose virtual CTP enhanced by computed tomography angiography seems to be under development (Tong *et al.*, 2014). Finally, the combination of computed tomography angiography with CTP, MTT and PS parameters may open a new era in human brain pathophysiology research.

To conclude, we have demonstrated that the advantages of carotid artery stenting are not limited to the CBF improvement. On the contrary, alleviation of hypoperfusion most likely modifies a wide number of parameters typical for prolonged ischaemia and related oxidative stress and inflammation. MTT measured 6–8 weeks after stenting provides an important predictive value with respect to MTT 36 months post stenting, suggesting a persistent improvement in the brain microcirculation. Diminished PS values may suggest a decline in the overall oxidative and inflammatory status that is maintained in both hemispheres for over 3 years after stenting. Further studies are required to validate our findings and determine their significance with respect to functional benefits for patients, such as improved cognition or stroke prevention.

Conflicts of Interest

The authors declare no conflict of interest.

Authorship

PJW and ASz contributed conception and design of the study; ASz and MK organized the database; MK performed the statistical analysis; PJW wrote the first draft of the manuscript; MK, GH, AS, KCh, MP, NK, ES, ASz wrote sections of the manuscript. All authors contributed to manuscript revision, had read and approved the submitted version.

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