



# Relative Cerebral Blood Transit Time Decline and Neurological Improvement in Patients After Internal Carotid Artery Stenting

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## Abstract

In this study we hypothesized that the alleviation of neurological symptoms long after

internal carotid artery (ICA) stenting may be related to sustained improvement of cerebral perfusion. Thirty-four subjects (F/M; 15/19)

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with >70% stenosis of a single internal carotid artery and neurological symptoms, who underwent a carotid artery stenting procedure, were studied. Brain computed tomography perfusion (CTP) imaging was performed before and 3 years after ICA stenting. The following relative variables were compared: cerebral blood flow (rCBF), cerebral blood volume (rCBV), mean transit time (rMTT), time to peak (rTTP), and permeability surface area product (rPS). A survey also was conducted to compare the patients' clinical symptoms. Overall, we found that a trend toward rMTT decline was the only persisting change after ICA stenting. We then stratified the patients into the subgroups of <2%, 2–5%, and > 5% rMTT decline and found that those with a rMTT decline >2% reported a prominent reduction in subjective clinical symptoms such as headache, dizziness, tinnitus, blurred vision, transient blindness, a sense of gravity of the head, and pain in the eyeballs. We conclude that a shortened mean rMTT, likely reflecting improved cerebral microcirculation, underlies the improvement of neurological symptoms in patients with ICA stenosis.

### Keywords

Blood transit time · Cerebral blood flow · Computed tomography perfusion · Internal carotid artery · Neurological symptoms

## 1 Introduction

Internal carotid artery (ICA) stenosis-related brain hypoperfusion is associated with neurological, psychiatric, and psychological deficits, manifesting as headache, dizziness, tinnitus, blurred vision, transient blindness, a sense of gravity in the head, and pain in the eyeballs. These symptoms associate with cognitive and mood decline. Neuropsychological deficits may not be as apparent as the neurological ones, but they add to the downgrading of quality of life. Numerous studies have demonstrated that ICA stenosis, without transient ischemic episodes or

strokes, is a detriment to executive functions and memory (Wang et al. 2016; Romero et al. 2009; Sztrihai et al. 2009; Popovic et al. 2011; Mathiesen et al. 2004). It has been demonstrated that cognitive function may improve in symptomatic patients after ICA recanalization, with both endarterectomy and carotid stenting (Yamashita et al. 2012; Chida et al. 2010). Interestingly, Grunwald et al. (2006) have shown cognitive improvements in word fluency and delayed recall in neuropsychological tests conducted 24 h after carotid artery stenting also in asymptomatic patients. Results, akin to those outlined above, have been reported by Wang et al. (2017) and Picchetto et al. (2013) in asymptomatic patients.

ICA stenosis is considered an independent risk factor for stroke (Goessens et al. 2007). It also contributes to the pathophysiology of depression (Rao et al. 2001; Mathiesen et al. 2004; Bakker et al. 2000), and it is a risk factor for suicides in stroke patients (Lovett and Rothwell 2002). According to Huang et al. (2012), ICA stenting relieves post-stroke depression in high-grade ICA stenosis patients over the time of 1 month. A therapeutic effect of stenting is superior to that exerted by selective serotonin reuptake inhibitors in these patients. In contrast, however, Picchetto et al. (2013) have observed no difference between pre- and post-scoring in the neuropsychological evaluation of depression and anxiety carried out in asymptomatic ICA stenosis patients subjected to stenting.

Cerebral blood flow (CBF), which may be assessed during computed tomography perfusion (CTP) examination, improves after ICA stenting (Szarmach et al. 2017; Frydrychowski et al. 2013; Trojanowska et al. 2006; Niesen et al. 2004). However, two other CTP-derived variables, namely, blood-brain barrier (BBB) permeability and mean transit time (MTT), are less recognized in the research and diagnosis of ICA stenosis. The BBB functioning is impaired, and the diffusion of fluid, blood, or contrast molecules into the extravascular space is augmented in the pathologic states such as neoplastic or inflammatory diseases, ischemia, and neurodegenerative disorders (Topakian et al. 2010; Jain et al. 2008). We have demonstrated that elevated BBB permeability can be reversed in

subjects with ICA stenosis after stenting (Szarmach et al. 2017). A disease-enhanced BBB permeability can be considered a radiological marker of neuroinflammation. A decline in BBB permeability with improvement of cerebral blood circulation, and thus increased delivery of oxygen to the brain tissue, suggests that the overall brain ischemic and inflammatory status improves.

Prolongation of MTT is increasingly linked to a cerebral small vessel disease (Arba et al. 2017; Cao et al. 2016). Such diseases, in turn, are associated with the accumulation of immune cells and erythrocytes in the brain microvessel lumina (Kaiser et al. 2014; Mencl et al. 2013; Schreiber et al. 2013; Rouhl et al. 2012; Schreiber et al. 2012). The MTT is prolonged in subjects with ICA stenosis (Szarmach et al. 2017). Importantly, acute MTT decline, 4–6 weeks after ICA stenting, sends a positive signal for the long-term MTT downward response (Winklewski et al. 2019). Thus, MTT decline after stenting strongly suggests the possibility of functional improvement in brain microcirculation.

Several authors have suggested that relative MTT (rMTT), which is the symptomatic hemisphere-to-asymptomatic hemisphere MTT ratio, may represent an early and sensitive parameter for the detection of perfusion changes (Duan et al. 2012; Merckel et al. 2012; Wilkinson et al. 2003). Consequently, we hypothesized that the long-term decline in rMTT after ICA stenting may be interrelated with the alleviation of neurological symptoms reported by patients.

## 2 Methods

### 2.1 Patient Population

There were 34 patients (F/M; 15/19) of the mean age of  $69.7 \pm 7.6$  years, suffering from ICA stenosis, investigated during 2010–2014 (Table 1). The patients were qualified for a carotid artery stenting procedure in the Department of Cardiac and Vascular Surgery of the Medical University of Gdansk in Poland.

A general neurological and internal examination of all the patients was performed before the

**Table 1** Risk factors and concomitant diseases in the population studied

Risk factor/disease	No. of cases
Smoker	15
Hypertension	34
Diabetes mellitus type 2	11
Transient ischemic attack	10
Stroke	5
Coronary artery disease	24
Lipid disorder	11
Myocardial infarction	14

stenting procedure. Patients with stenosis of more than 70% within a single internal carotid artery and with concomitant neurological symptoms (i.e., headache, dizziness, tinnitus, blurred vision, transient blindness, a sense of gravity of the head, and pain in the eyeballs) were included in the study. In all patients, duration of carotid artery stenosis was longer than 5 years. The degree of artery stenosis, according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET 1991), was evaluated using Doppler ultrasonography and confirmed immediately prior to stent implantation by digital subtraction angiography (DSA). Only were patients with a complete circle of Willis and normal vertebral arteries included in the evaluation.

Patients with bilateral hemodynamically significant (i.e., >70%) stenosis of cranial arteries, patients with complete occlusion of one vessel, or those who had experienced extensive ischemic brain stroke were excluded from the study. Consequently, in the patients included in the study, stenosis on the contralateral side was hemodynamically insignificant (i.e., <50%). Patients with abnormal blood pressure, heart rate values, uncontrolled hyperthyroidism, renal insufficiency, hypersensitivity to iodine, or a history of adverse effects following the administration of contrast agents were also excluded from the study.

### 2.2 Imaging Protocol

The imaging protocol of the study included a Doppler examination, non-contrast axial computed tomography, CTP, and DSA. All

images are taken before and after the injection of an iodinate contrast medium. The DSA, as a gold standard in neuroradiology, is performed in patients with various types of vascular pathology, such as aneurysm, arteriovenous malformation, fistula, and vessel occlusion or stenosis. This radiographic technique visualizes cerebral vessels with the minimum view of a background tissues.

The CTP imaging was performed before and 3 years after ICA stenting. The imaging was done using a 64-MDct Light Speed VCT XT scanner (GE Healthcare Technologies, Waukesha, WI). Non-contrast axial computed tomography scans allowed for the identification of signs of active bleeding, acute ischemic stroke, or features of increased intracranial pressure. The axial images acquired for CT perfusion at 40 mm in cine mode (CTP 4 cm) were initiated 5 s after the start of 40 mL of the nonionic iodine-based intravascular contrast agent, OPTIRAY 350 (Mallinckrodt, St. Louis, MO), administered into an antecubital vein at an injection rate of 4 mL/s. After contrast injection, an additional bolus of 40 mL of physiological saline was administered. The acquisition parameters for the CT examinations were the following: tube voltage 80 kV, 150 mAs, slice thickness 5 mm, rotation time 1/s, field of view (FOV) 25 cm, time interval between reconstructed images 0.5–1 s, total exposure time 45 s, interval 0.5 mm, gantry angle parallel to and above the orbital roof to avoid radiation exposure to the lens, image matrix 512 x 512, and eight slices. A total of 272 slices from 34 patients were obtained, with a scan time of 45 s.

The arterial input function was chosen within the anterior cerebral artery (segment A2) on the basal ganglia level. The venous output region was selected from the superior sagittal sinus. All of the listed acquisition parameters were applied as provided by the manufacturer for the brain perfusion study.

### 2.3 Image Post-processing

The raw data were transferred to a dedicated diagnostic workstation (AW 4, GE Healthcare Technologies, Waukesha, WI) and analyzed

using a research version of the CTP post-processing software package (CT Perfusion v4.3.1) (GE Healthcare Technologies, Waukesha, WI) to create color maps of dynamic cerebral enhancement, represented as CBF, cerebral blood volume (CBV), mean transit time (MTT), time to peak (TTP), and permeability surface area product (PS).

This diagnostic application offers two different evaluation modes. The first mode, the “neuro-brain stroke” mode, calculates the perfusion metrics of MTT, CBF, CBV, and TTP for brain stroke assessment using the maximum slope method (Lin et al. 2007; Fiorella et al. 2004). The MTT characterizes the average time of contrast agent residence within the tissue. In mathematical terms, the mean transit time is computed as the time between the initial impulse and the time of arrival. The MTT is computed and displayed in seconds. The CBF is derived from the initial value of the impulse residue function and is computed and displayed in mL *per* 100 g of wet tissue *per* minute. The CBV is computed and displayed in mL *per* 100 g of wet tissue. The blood volume is the product of blood flow and mean transit time:  $CBV = CBF \times MTT$ . The TTP is the time between the onset of enhancement transient (last pre-enhancement image) and the peak value of time curve (image with the maximum value before the first post-enhancement image). The time to peak is computed and displayed in seconds, using the raw time curve data directly.

The second mode, known as the “neuro-brain tumor” mode, calculates microvascular permeability (PS) and fractional blood volume based on the Johnson and Wilson model (St Lawrence and Lee 1998a, b). The PS is computed and displayed in mL *per* 100 g of wet tissue *per* minute. It is computed from the impulse residue function. Contrast agent diffusion appears in the impulse residue function as a residual enhancement that occurs after the initial impulse response and decreases exponentially with time.

Two experienced neuroradiologists blinded to clinical information (medical history, side, and time of operation) independently manually drew two standardized elliptical mirrored regions of interest (ROI). The ROI (approximately 10 cm<sup>2</sup> each) was determined on all analyzed levels, over

the cortical gray matter centered 20 mm from the brain edge. The large vessels were automatically excluded via brain perfusion software. The absolute values of CTP parameters (MTT, TTP, CBF, CBV, and PS) of one hemisphere in the region of middle cerebral artery distribution and contralateral mirroring areas in functional maps were measured. Then, the relative parameters were calculated as the symptomatic hemisphere-to-asymptomatic hemisphere ratios.

## 2.4 Patient Surveys

A survey was given to patients who qualified for the stenting procedure. The first survey was carried out on the day of admission. The second survey was performed after the follow-up perfusion scan (approximately 3 years after the procedure). The following questions were asked:

- Headache: Yes/No
- Dizziness: Yes/No
- Tinnitus: Yes/No
- Blurred vision: Yes/No
- Transient blindness: Yes/No
- A sense of gravity of the head: Yes/No
- Pain in the eyeballs: Yes/No

## 3 Results

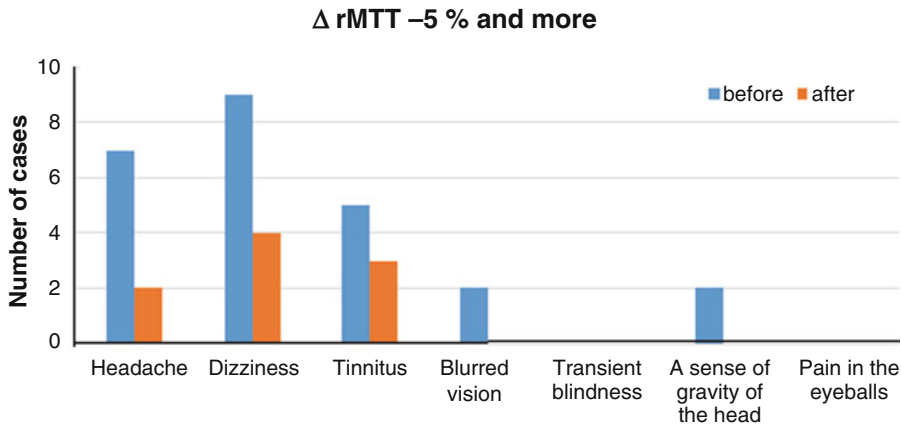
Relative CBF, CBV, MTT, TTP, and PS values did not change 3 years after stenting, compared to the baseline values measured before stenting (Table 2). Nevertheless, a clear trend toward rMTT decline was observed. When a subgroup analysis was performed, it appeared that three separate groups of patients could be distinguished: (1) patients with rMTT decline greater than 5%, (2) patients with rMTT decline between 2% and 5%, and (3) patients with rMTT decline less than 2%. Improvement in clinical symptoms, reported by patients, was related to a decline in rMTT. A prominent improvement was reported with a rMTT decline greater than 2% (Figs. 1, 2, and 3).

In the group with the greatest rMTT decline, the number of reported headaches was reduced from 7 to 2, dizziness from 9 to 4, tinnitus from 5 to 3, blurred vision from 4 to 2, transient blindness from 2 to 1, a sense of gravity of the head from 2 to 0, and pain in the eyeballs from 3 to 1. In the group with rMTT decline between 5% and 2%, the number of reported headaches was reduced from 9 to 3, dizziness from 7 to 3, tinnitus from 11 to 4, and blurred vision and a sense of gravity of the head from 2 to 0.

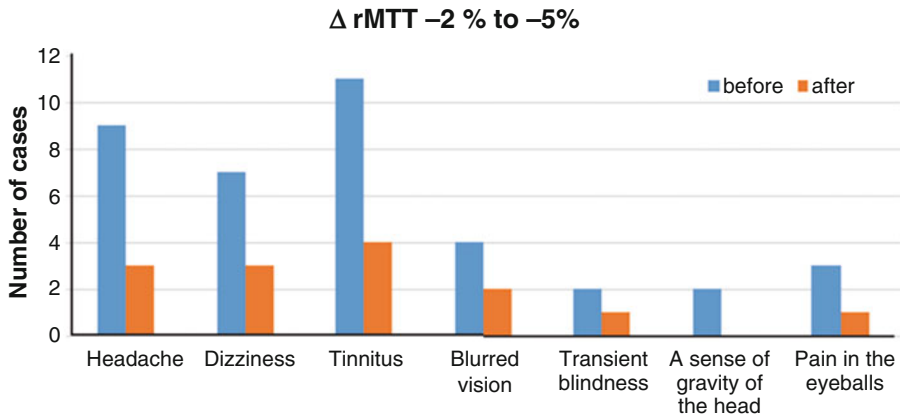
**Table 2** Comparison of computed tomography perfusion (CTP) at baseline before stenting and 36 after stenting

Parameter	Parametric <i>t</i> -test for dependent samples ( <i>n</i> = 34)		
	Mean ± SD (median)	Δ change	<i>p</i>
rMTT <sub>1</sub>	1.09 ± 0.27 (1.06)	−7.59%	0.155
rMTT <sub>3</sub>	1.01 ± 0.20 (0.99)		
rCBV <sub>1</sub>	0.96 ± 0.19 (0.96)	+6.56%	0.134
rCBV <sub>3</sub>	1.02 ± 0.15 (1.03)		
rCBF <sub>1</sub>	0.99 ± 0.09 (1.01)	+1.11%	0.563
rCBF <sub>3</sub>	1.00 ± 0.07 (1.00)		
rTTP <sub>1</sub>	1.01 ± 0.03 (1.01)	+2.08%	0.515
rTTP <sub>3</sub>	1.03 ± 0.19 (1.00)		
rPS <sub>1</sub>	1.09 ± 0.34 (1.06)	+0.74%	0.905
rPS <sub>3</sub>	1.10 ± 0.24 (1.06)		

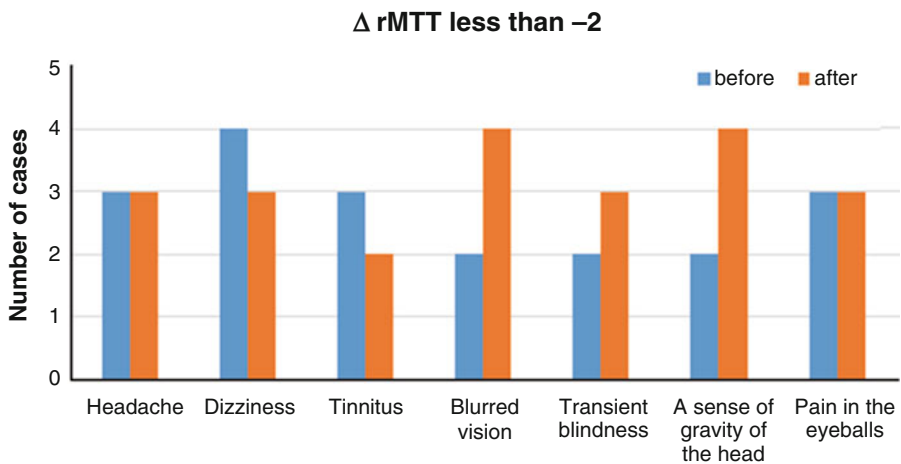
MTT mean transit time, CBV cerebral blood volume, TTP time to peak, and PS permeability surface area product; “r” stands for “relative” parameters that were calculated as symptomatic hemisphere-to-asymptomatic hemisphere ratios; “1” denotes parameters at baseline before stenting; and “3” denotes parameters 3 years after stenting procedure



**Fig. 1** Changes in clinical symptoms in patients with internal carotid artery (ICA) stenosis, associated with relative mean transit time (rMTT) decline greater than 5%, 3 years after the stenting procedure  $\Delta$



**Fig. 2** Changes in clinical symptoms in patients with internal carotid artery (ICA) stenosis, associated with relative mean transit time (rMTT) decline between 2% and 5%, 3 years after the stenting procedure



**Fig. 3** Changes in clinical symptoms in patients with internal carotid artery (ICA) stenosis, associated with relative mean transit time (rMTT) decline less than 2%, 3 years after the stenting procedure

In contradistinction, in patients without an appreciable decline in rMTT (<2%), clinical symptoms either did not change or actually worsened (Fig. 3). In this group, the number of reported headaches remained unchanged (3 cases before and after ICA stenting), dizziness decreased from 4 to 3, tinnitus from 3 to 2, blurred vision increased from 2 to 4, transient blindness increased from 3 to 4, a sense of gravity of the head increased from 2 to 4, and pain in the eyeballs remained unchanged (3 cases before and after ICA stenting).

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## 4 Discussion

The main finding of the study is that relative decreases in MTT were associated with improvements in the clinical symptoms reported by patients with ICA stenosis, 3 years after the stenting procedure, providing that the decreases were greater than 2% of the baseline level noted before stenting. Taking into account both objective measurements and self-assessed symptoms allows for a more complete evaluation of the influence of the stenting procedure. In the literature, CBF is the most often used variable for the evaluation of treatment effects in patients with ICA stenosis. There is a need to focus on the influence of treatment on the perception of quality of life, especially for the extended periods of time, longer than a year (Shan et al. 2015). The assessment of quality of life can be helpful in the estimation of the effectiveness of treatment in terms of stroke prevention and in comparison of different types of treatments, and as such it is an important therapeutic goal (Fadrná et al. 2018). Assessing quality of life in this group of patients is also vital, since the very presence of severe carotid stenosis may predispose patients to lower general well-being and lower satisfaction with life, let alone depressive and cognitive impairment (Pucite et al. 2017).

There is an ongoing discussion regarding the pathomechanisms involved in cerebral small vessel disease and the subsequent development of neurological symptoms and cognitive decline. According to some authors, vascular stiffening,

increased pulse pressure, and carotid pulsatility are the major factors leading to the development of white matter hyperintensities and neurological and cognitive deterioration (Wardlaw et al. 2017; van Sloten et al. 2015; Aribisala et al. 2014; Singer et al. 2014). There is a contradicting theory, indicating that a prolonged brain hypoperfusion results in hypoxia, inflammation, and oxidative stress, followed by a blood-brain barrier collapse (Ding et al. 2017; Duncombe et al. 2017; Szarmach et al. 2017; Kim et al. 2012).

In this study we demonstrated that subjective symptoms reported by patients might be related to changes in cerebral microcirculation. Consequently, our study refocuses clinical attention on the interventional and non-interventional medical procedures aiming to maintain blood flow in cerebral small vessels, such as carotid artery recanalization, proper pharmacological therapy, and lifestyle modifications. The predominant notion of numerous reports is that MTT is the most sensitive marker of cerebral perfusion changes. However, calculation of accurate absolute values of this parameter is impractical, while using absolute threshold values in making therapeutic decisions is dubious due to the parameter's strong correlation with numerous external factors, e.g., cardiac output, age, or a degree of stenosis (Zhang et al. 2013; Esteban and Cervera 2004; Koenig et al. 2001). Consequently, we assessed relative MTT in this study, i.e., the ratio of symptomatic hemisphere-to-asymptomatic hemisphere MTT.

ICA stenosis was diagnosed in all patients by a Doppler examination more than 5 years before surgery. Due to stringent inclusion criteria, consisting of <70% stenosis within a single ICA, the population of this study was homogeneous in terms of cerebral hemodynamic parameters and was characterized by low CBF and low CBV. As a result, ICA stenosis on the contralateral side must have been hemodynamically insignificant (<50%), as evidenced by other studies (Ricotta et al. 2011; Nicolaidis et al. 2005; Samson et al. 1999). Patients with bilateral hemodynamically significant, i.e., >70%, stenosis of the cranial arteries were excluded from the study. Although a relatively narrow population can be seen a limitation of this study, its

homogeneity could enhance the reliability of results. The present findings justify further research with the use of magnetic resonance imaging (MRI). In particular, a combination of dynamic susceptibility contrast MRI (DSC-MRI), dynamic contrast-enhanced MRI (DCE-MRI), and blood oxygen level-dependent imaging MRI (BOLD-MRI) could provide comprehensive information on the effect on the functional brain status of cerebral microcirculation and blood-brain barrier permeability fluctuations. Such studies with the concomitant neuropsychological assessment are currently under way.

Quantitative CTP data are highly dependent on the post-processing software. Software differences are frequently considered the main cause of variability in perfusion results relative to inter-operator and intra-operator differences (Kudo et al. 2010; Kamalian et al. 2011; Zussman et al. 2011). In this study we used the equipment manufactured by one producer and the same post-processing procedure for all subjects. Further, there were two experienced neuroradiologists who independently drew standardized elliptical mirrored ROIs, with the area of approximately 10 cm<sup>2</sup> each, on the section level of the reference CT image over the cortical gray matter of the middle cerebral artery territory. Finally, in all subjects, we used a coverage size of 40 mm, which is well-suited for detecting perfusion parameters owing to the high density of scans (Szarmach et al. 2016).

In conclusion, we believe we have conclusively demonstrated in this study that subjective symptoms reported by patients suffering from ICA stenosis might be related to changes in cerebral microcirculation. Further studies with the extensive use of various MRI techniques are warranted to assess how changes in the brain microcirculation and blood-brain barrier functional status are related to patients' self-reported quality of life and to overall patients' functional status.

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**Conflicts of Interest** The authors declare no conflicts of interest in relation to this article.

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The experimental protocol of the study was approved by the Ethics Committee of the Medical University in Gdansk, Poland.

**Informed Consent** Written informed consent was obtained from all individual participants included in the study.

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