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TRANSCRANIAL DUPLEX ULTRASONOGRAPHY MEASUREMENTS TOWARDS IDENTIFICATION OF BLOOD VESSEL CONDITIONS: ARTIFICIAL CEREBRAL BLOOD FLOW IN PATHOLOGIES

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The aim of the study was to investigate how cerebral vasospasm, vasodilation and haemorrhage under artificial circulation conditions during cardiopulmonary bypass affect transcranial duplex ultrasonography measurements. A description of transcranial duplex ultrasonography and phantom development is provided. Measurements were made using a commercially available ultrasound system and cardiopulmonary bypass machine, water phantom and 32% glycerol solution with cornstarch. The experiments showed that the cerebral blood vessel condition in artificial circulation affects transcranial duplex ultrasonography measurement limit values. The most sensitive parameter for blood vessel condition changes is Peak Systolic Velocity (PSV) for which changes were observed in 100% of cases. The most insensitive was Time-Averaged Peak-Velocity (TAPV), and Minimum Diastolic Velocity (MDV) for which changes were observed in 83% of cases.

Keywords: *artificial blood, cardiopulmonary bypass machine, brain phantom, neuroprotection, cerebral autoregulation.*

INTRODUCTION

Open human heart surgeries are performed every day around the world — for example, 110 000 heart valve surgeries and 3400 heart transplants are performed annually in the United States of America (Weiss and Elixhauser, 2014). A cardiopulmonary bypass machine made possible open-heart surgery, specifically for coronary artery bypass, heart valve repair or replacement, arrhythmia surgery, aneurysm repair, transmyocardial laser revascularisation, heart transplantation. The cardiopulmonary bypass machine is able to take over the functions of the heart and lungs, thus ensuring blood circulation and gas exchange in the body, when the heart is stopped for the operation.

The purpose of the cardiopulmonary bypass machine is to connect to the patient's blood circulatory system through venous cannulas in the upper and lower vena cava, and transport blood from the upper-right heart chamber (the right atrium) to a special reservoir called an oxygenator. Inside the oxygenator, oxygen bubbles up through the blood and enters the red blood cells, which leads to oxygen saturation of the blood. Then, a filter removes air bubbles from the oxygen-rich blood, and the blood travels through a tube

to an arterial cannula in the aorta, from where it moves throughout the body, delivering oxygen to human tissues.

The heart-lung machine can take over the work of the heart and lungs for hours, but the amount of time a patient is under the cardiopulmonary bypass machine should be limited as much as possible because prolonged use can lead to post-perfusion syndrome, which is dysfunction of various organs and systems after cardiopulmonary bypass, and, occasionally, after other operative procedures in which large quantities of blood are transfused (Liumbruno *et al*., 2011). Problems include heart failure (systolic and diastolic), disorders of the haemostasis system (coagulopathy and platelet dysfunction) and brain disorders (neurocognitive dysfunction, brain infarct, haemorrhage). Therefore, it is very important to control the cerebral blood flow to avoid the development of cerebral dysfunction, which causes are vasospasm, vasodilation and haemorrhage (Dvoryanchikova *et al*, 2017).

The effect of various pathological cerebral blood vessels conditions and physiological parameters of blood on its flow have been studied using transcranial duplex ultrasonography measurements (Kulikov, 2007; Purkayastha and Sorond, 2012; Topcuoglu, 2012; Bathala et al., 2013). However, the influence of blood vessel conditions on the blood flow by the cardiopulmonary bypass machine has not been studied. It is possible to study these effects using *in vitro* experiments.

The purpose of this study was to evaluate the correlation between blood flow velocity and vasospasm, vasodilation and haemorrhage of blood vessels. The study focuses on head vessels.

MATERIALS AND METHODS

Brain ultrasound phantom. In order to obtain precise transcranial duplex ultrasonography measurements, the acoustic properties of the ultrasound head phantom must correspond to the properties of human tissues. After comparing the acoustic properties of the available brain modelling materials, PP plastic (container, 200 mm × 200 mm) was chosen for human skull modelling, and silicone and water phantom were chosen for brain modelling (Singh, 2003; Culjat *et al*., 2010; Zhang, 2013). However, the silicone phantom did not pass the initial ultrasound test because the adhesion of silicone and plastic (PP) was insufficient and ultrasound did not pass through the boundary of these media. In the case of water phantom, no problems related to ultrasound permeability were found — on B-mode the water medium appeared as a homogeneous background; carbonated water could be used to create an inhomogeneous background, which is typical for human tissues. Tap water was used to provide brighter visibility of the target, which was blood vessels.

The fixation of the artificial blood vessels is the only working problem with the water ultrasound phantom. During the operation of the cardiopulmonary bypass machine, small vibrations were created that moved the blood vessel. During measurement, displacement of the insonated blood vessel can affect measurements, so proper attention should be paid to fixation.

The middle cerebral artery is the most frequently insonated artery during transcranial duplex ultrasonography because it receives approximately 60–70% of the blood from the internal carotid artery, which allows to assess the blood flow characteristics in one hemisphere of the brain (Kulikov, 2007). The path to the cerebral arteries consists of the aortic arch and the common carotid artery, which branches into two arteries, the internal and external carotid arteries. The internal carotid artery extends to the middle cerebral artery and then to even smaller cerebral arteries, and the external carotid artery branches into smaller cerebral blood vessels. Silicone tubes were chosen after studying the physical parameters of the blood vessels, but the lumen diameter was slightly different from the anatomical dimensions of the blood vessels. Therefore, using the Hagen–Poiseuille equation and pressure values in the blood vessels, the optimal blood vessel length was calculated, such that the hydraulic resistance corresponded to the physiological — the common carotid artery (Ø9.5 mm × 120 mm), internal carotid artery (Ø6.7 mm × 90 mm), external carotid artery (Ø6.7 mm × 90 mm), other cerebral arteries (Ø6.7 mm × 80 mm), and middle cerebral artery (Ø3.4 mm × 109 mm) (Evangelista *et al.*, 2010; Limbu *et al.*, 2006; Choudhry, 2016; Schreiber *et al.*, 2000; Blanco *et al.*, 2017). A schematic representation of the circulatory system is demonstrated in Figure 1.

Blood mimicking fluid. Usually, studies have used a mixture of glycerol and water as a blood mimicking fluid for doppler ultrasound phantoms. Thus, we also used a 32% glycerol solution with properties corresponding to the rheological properties of human blood at 37 ^{o}C: fluid density 1053 kg/m^3 and fluid viscosity 3–4 mPa/s (Oglat *et al*, 2018; Samavat and Evans, 2006). The blood-mimicking fluid corresponded to the viscosity of the human blood, shown using the test method described in the standard ASTM D445/D446, ISO 3104/3105. The properties corresponded to the blood at 37 ^{o}C, but in modern perfusiology different temperature modes are used. Presently, there is still discussion on the advantages and disadvantages of one or another mode, as well as their consequences.

To reflect the ultrasound signal, corn starch was used as the model of erythrocytes. The density and particle size of corn starch correspond to the physical parameters of erythrocytes, which have particle size 7–8 mkm. Other studies used a particle size of 3–70 mkm (Oglat *et al*, 2018; Samavat and

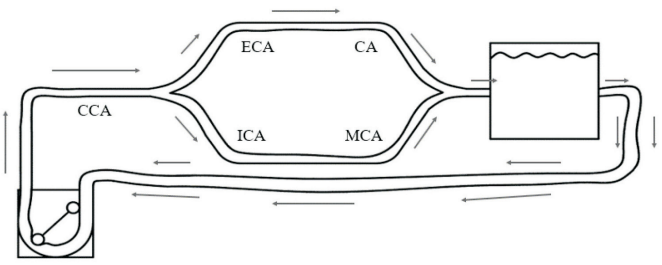

Fig. 1. Schematic representation of the circulatory system in the phantom.

Evans, 2006). In our study the particle size was 5–10 mkm and particle density — 1010–1090 kg/m^3.

Transcranial duplex ultrasonography measurements. The artificial circulatory system was installed in the brain phantom and filled with blood mimicking fluid through a reservoir (drainage bag, 1.5 l). The cardiopulmonary bypass machine STOCKERT SIII System (Stockert GmbH, Freiburg im Breisgau, Germany) was connected to the artificial circulatory system through a set of plastic tubes. During surgery, the fluid supply for each patient is calculated separately, to maintain the vital functions of the body. The fluid supply for an adult is 70 ml/min/kg. This fluid supply is for the whole body, but only the blood circulation in the brain was modelled in the study. Therefore, the fluid supply was only 15% of the total blood volume, corresponding to fluid supply of 1 l/min and body mass 90 kg.

An ultrasound sonography PHILIPS EPIQ 7 (Philips, Eindhoven, Netherlands) with a 3040-element sector array probe *X5-1* (frequency range 1–5 MHz) was used to study correlation between pathological blood vessels conditions in the brain phantom and transcranial duplex ultrasonography measurements under artificial blood flow. The study was carried out with automatic angle correction equal to 60^o.

The sonography automatically delivered measurement of peak systolic velocity (PSV), end-diastolic velocity (EDV), minimum diastolic velocity (MDV), time-average peak-velocity (TAPV), resistive index (RI) and pulsatility index (PI). Was used only PSV, MDV and TAPV parameters in this study, since the others are closely related to systole and diastole, and in artificial circulation both parameters are absent.

Transcranial duplex ultrasonography measurements were performed for three pathological blood vessels conditions (vasospasm, vasodilation, and haemorrhage) in the brain phantom at different locations (proximal and distal to the pathology). Also, the effects of pathology severity (25%, 50%, and 75%) on transcranial duplex ultrasonography measurements were studied for two pathological blood vessels conditions (vasospasm and vasodilation). These degrees of pathology severity were chosen based on previous research — the most common size of vasodilation is 3–6 mm with interval 4.2–6 mm, which was modelled a fusiform vasodilation (Jeong *et al*., 2009). The vasospasm interval in this study was 2.6–0.9 mm.

RESULTS

The obtained measurements in the experiment (proximal and distal to vasospasm of different severity) are demonstrated in Figures 2 and 3, which show the dependence of blood flow velocity on the vasospasm severity. Dopplergrams characterising the blood flow proximal and distal to the pathology are shown in Figure 4 (A-G).

Under artificial circulation conditions, there was a significant (F-criterion, α = 0.05) non-linear correlation between

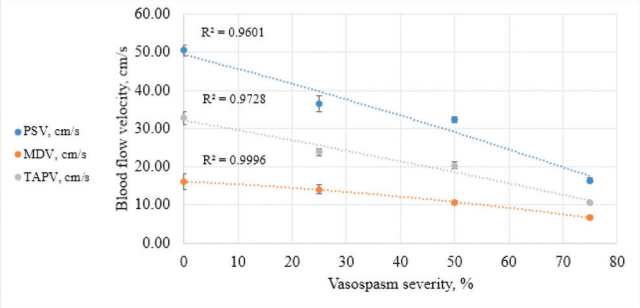

Fig. 2. Dependence of proximal blood flow velocity in artificial circulation on the vasospasm severity. PSV, Peak Systolic Velocity; MDV, Minimum Diastolic Velocity; TAPV, Time-Averaged Peak-Velocity.

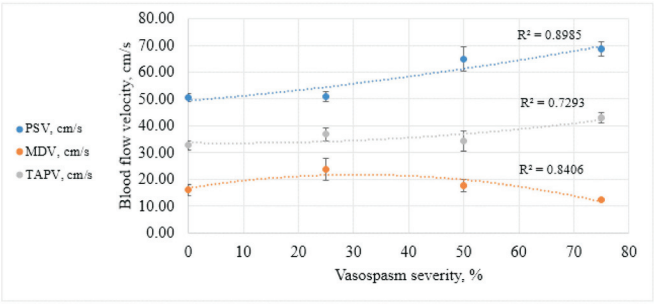

Fig. 3. Dependence of distal blood flow velocity in artificial circulation on the vasospasm severity. For abbreviations see Fig. 2.

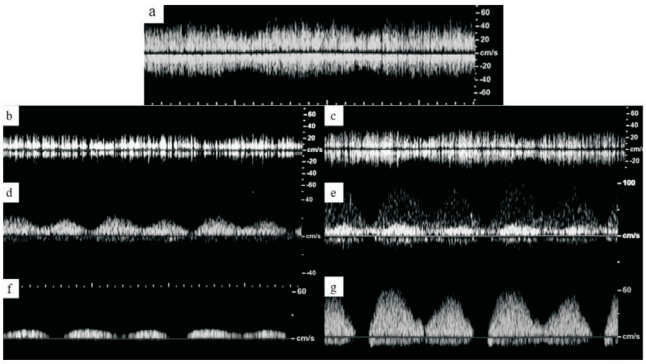

Fig. 4. (a) Artificial cerebral blood flow dopplergrams in the conditionally healthy blood vessels; b(b) proximal artificial cerebral blood flow dopplergrams in 25% vasospasm; (c) distal artificial cerebral blood flow dopplergrams in 25% vasospasm; b(d) proximal artificial cerebral blood flow dopplergrams in 50% vasospasm; (e) distal artificial cerebral blood flow dopplergrams in 50% vasospasm; (f) proximal artificial cerebral blood flow dopplergrams in 75% vasospasm; (g) distal artificial cerebral blood flow dopplergrams in 75% vasospasm.

the severity of vasospasm and blood flow velocity parameters (PSV, MDV, TAPV) proximal to the vasospasm. Under artificial circulation conditions, when the severity of vasospasm increased in the range from 0 to 75%, blood flow velocity parameters of proximal vasospasm values decreased (PSV: from 50.49 ± 1.39 cm/s to 16.44 ± 0.63 cm/s, MDV: from 16.11 ± 2.09 cm/s to 6.66 ± 0.42 cm/s, TAPV: from 32.69 ± 1.80 to 10.58 ± 0.30 cm/s). It was concluded that in the proximal part of the blood vessel, vasospasm has the greatest effect on TAPV.

Changes in blood flow PSV value proximal and distal to the pathology were also well observed on dopplergrams, which

shows how much vasospasm affects the doppleram signal form. With increasing severity of vasospasm there were oscillations of amplitude, which were more pronounced in the distal part of the blood vessel. The dopplergram in the case of 75% vasospasm showed that there was transient obstruction of the blood flow proximal and distal to the pathology.

Under artificial circulation conditions, there was a significant (F-criterion, $\alpha = 0.05$) non-linear correlation between the severity of vasospasm and blood flow velocity parameters (PSV and MDV) distal to the vasospasm. Under artificial circulation conditions, when the severity of vasospasm increased in the range from 0 to 75%, blood flow velocity PSV of distal vasospasm increased (PSV: from 50.49 ± 1.39 cm/s to 68.58 ± 2.69 cm/s. MDV slightly increased (from 16.11 ± 2.09 cm/s to 23.74 ± 4.02 cm/s in the vasospasm range from 0 to 25%) and then decreased (to 12.43 ± 0.40 cm/s). In the case of TAPV, no statistically significant correlation was found. It was concluded that in the distal part of the blood vessel, vasospasm has the greatest effect on the PSV parameter.

Measurements obtained in the experiment (proximal and distal to vasodilation of different severity) are demonstrated in Figures 5 and 6, which show the dependence of blood flow velocity on vasodilation severity, also shown in dopplergrams characterising the blood flow proximal and distal to the pathology, Figure 7 (A–F).

Under artificial circulation conditions, there was a significant (F-criterion, $\alpha = 0.05$) non-linear correlation between the severity of vasodilation and blood flow velocity parameters (PSV and MDV) proximal to the vasodilation. Under artificial circulation conditions, when the severity of vasodilation increased in the range from 0 to 75%, blood flow velocity PSV of proximal vasodilation decreased (PSV: from 50.49 ± 1.39 cm/s to 35.34 ± 1.37 cm/s). MDV slightly increased (from 16.11 ± 2.09 cm/s to 23.67 ± 3.02 cm/s in the vasodilation range from 0 to 50%) and then decreased (to 17.88 ± 2.25 cm/s). In the case of TAPV, no statistically significant correlation was found. It was concluded that in the proximal of the blood vessel, vasodilation has the greatest effect on PSV.

The changes are not strongly pronounced on the dopplergrams. In general, the dopplergrams are not clearly different depending on the severity of vasodilation.

Under artificial circulation conditions, there was a significant (F-criterion, $\alpha = 0.05$) non-linear correlation between the severity of vasodilation and blood flow velocity parameters (PSV and TAPV) distal to the vasodilation. Under artificial circulation conditions, when the severity of vasodilation increased in the range from 0 to 50%, blood flow velocity parameters of distal vasodilation decreased (PSV: from 50.49 ± 1.39 cm/s to 28.13 ± 2.11 cm/s, TAPV — from 32.69 ± 1.80 to 21.51 ± 2.73 cm/s) and then values increased (PSV: to 33.06 ± 1.25 cm/s, TAPV: to 24.95 ± 2.01 cm/s). There was no statistically significant effect of severity of vasodilation on MDV. It was concluded that in the

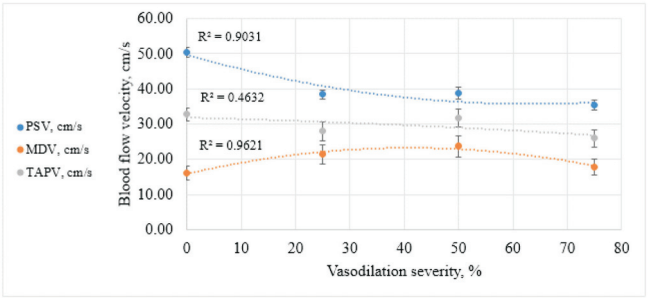

Fig. 5. Dependence of proximal blood flow velocity in artificial circulation on the vasodilation severity. For abbreviations see Fig. 2.

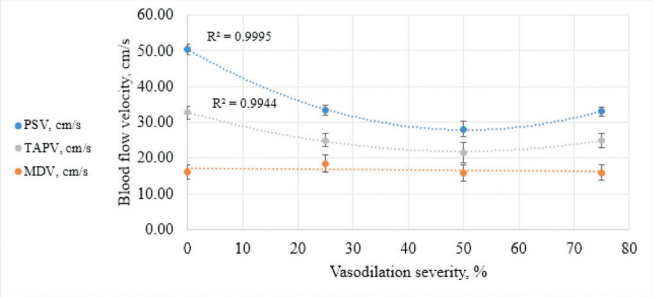

Fig. 6. Dependence of distal blood flow velocity in artificial circulation on the vasodilation severity. For abbreviations see Fig. 2.

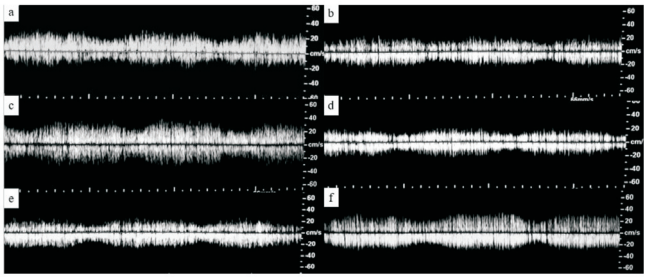

Fig. 7. (a) Proximal artificial cerebral blood flow dopplergrams in 25% vasodilation; (b) distal artificial cerebral blood flow dopplergrams in 25% vasodilation; (c) proximal artificial cerebral blood flow dopplergrams in 50% vasodilation; (d) distal artificial cerebral blood flow dopplergrams in 50% vasodilation; (e) proximal artificial cerebral blood flow dopplergrams in 75% vasodilation; (f) distal artificial cerebral blood flow dopplergrams in 75% vasodilation.

distal part of the blood vessel, vasodilation has the greatest effect on PSV parameter.

The obtained results in the experiment (proximal and distal to the haemorrhage) are demonstrated in Figure 8. The blood flow velocity proximal to the pathology increased sharply, forming a strong oscillation of the amplitude (Fig. 9 (A–B)), because the difference between the maximum and minimum velocity was large. The blood flow distal to the pathology had a higher velocity than in physiologically healthy blood vessels, but less than in the proximal part of the blood vessel. The dopplergram also shows oscillation of the amplitude of the blood flow velocity.

It was concluded that under artificial circulation conditions, blood flow velocity in the proximal and distal parts of the cerebral phantom is significantly ($\alpha = 0.05$) affected by

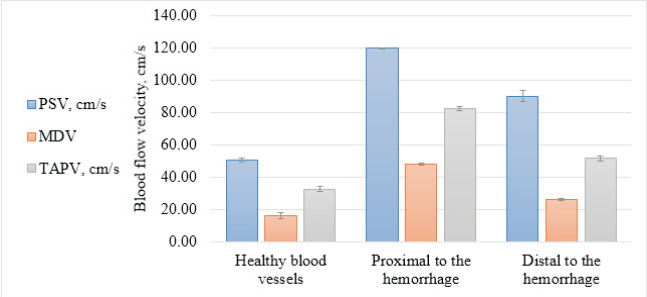

Fig. 8. The effect of insonation location on the artificial blood flow velocity. For abbreviations see Fig. 2.

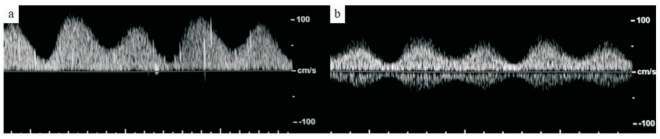

Fig. 9. (a) Proximal artificial cerebral blood flow dopplergrams in haemorrhage; (b) distal artificial cerebral blood flow dopplergrams in haemorrhage.

haemorrhage. Under artificial circulation conditions, blood flow velocity in the proximal part of the cerebral phantom blood vessel was higher than blood flow velocity in the distal part (PSV: 1.33 times higher, MDV: 1.82 times higher, TAPV: 1.60 times higher). It was concluded that blood flow velocity had the greatest influence on the MDV parameter.

DISCUSSION

In this study, we investigated the effect of pathological blood vessel conditions on artificial blood flow using transcranial duplex ultrasonography. Artificial blood flow velocities and dopplergrams were measured in blood vessels with vasospasm, vasodilation, and haemorrhage, using a brain phantom. The ultrasonography values were compared with the results of a conditionally healthy blood vessel and with each other. The transcranial duplex ultrasonography parameters (blood flow velocity and dopplergram) in a blood vessel with vasospasm were demonstrated in Figures 2–4. Vasospasm severity affects the dopplergram signal form, increasing the amplitude as the particles expend more energy to cross the high resistance area. When a certain resistance value is reached, a temporary occlusion occurs, meaning that the energy, which the pump gives to the particles, is insufficient to cross this high resistance area. Amplitude oscillations are formed because the cardiopulmonary bypass machine uses a peristaltic pump, which initially generates a flow with small oscillations (they can also be seen on the blood flow dopplerogram in the conditionally healthy blood vessels, Fig. 4 (A)). With vasospasm the oscillations become more evident.

Studies have demonstrated that blood flow velocity increases (significant focal increase of the PSV) in blood vessels with vasospasm (Topcuoglu, 2012). Thus, the results of this study showing that as the severity of vasospasm increases, the blood flow velocity estimated by PSV in the distal part to the pathology increases, are supported by earlier studies of the vasospasm effect on physiological blood flow. Also. it is known that in the physiological flow the vasospasm severity at first does not greatly affect the blood flow velocity, but at 20% vasospasm severity, the blood flow velocity changes more rapidly (Kulikov, 2007).

In the case of artificial blood flow in the blood vessel with vasodilation, however, no statistically significant changes were found. This is related to the small size of the blood vessel diameter. Some studies have shown that the diagnostic performance with the vasodailation size ≤ 5 mm is worse than with larger vasodilation (White *et al*, 2000). Thus, no significant changes in the artificial blood flow could be observed at such small diameters.

In the case of haemorrhage, the proximal artificial blood flow velocity was greater than the distal blood flow velocity, because the pressure gradient increased in the haemorrhage area, thereby increasing the blood flow velocity proximal to the pathology. The distal blood flow velocity decreases as the particles expend energy to cross the area.

During measurement, the spectral broadening artefact was checked, which is the result of varying angles to flow when the transmitting region of the transducer (the aperture) is not approximated by a point source. The spectral broadening artefact is exacerbated at large Doppler angles. Experimentally changing the tilt angle did not greatly affect the spectral window.

Also, in most cases, reverse blood flow was observed on the dopplergrams, which is a spectral mirroring artefact, since the form of the reverse blood flow dopplergram completely repeats the forward blood flow. This artefact is most likely due to the fact that the Doppler angle is close to 90 degrees (as flow is detected in both directions simultaneously). Therefore, it is very important to fix the Doppler sensor at an angle from 45 to 55 degrees. As an alternative the transmitting power and/or receiver gain can be reduced, but care must be taken as the actual signal can also be adversely affected. Also, as a recommendation, proper attention should be paid to the fixation of the Doppler sensor, such that measurements are taken from the same location proximal and distal to the pathology.

This study was conducted with a limited number of vasospasm and vasodilation severities and limited number of factors. Therefore, further work on transcranial duplex ultrasonography under artificial blood flow conditions and the dependence of estimated parameters on the cerebral blood vessel conditions may include more numbers of severities and factors like changes in blood temperature and the Doppler sensor tilt angle.

The obtained blood flow velocities in conditionally healthy blood vessels differ from physiological parameters approximately by twice. The average value of maximum blood flow velocity in the middle cerebral artery in a healthy person is 100 cm/s, while the average value of blood flow velocity under artificial blood flow conditions in a healthy blood vessel is 50 cm/s (Kulikov, 2007). The dopplergram

signal form is also different. Further work should be aimed at creating an artificial blood circulation device with more physiological flow parameters.

Future research is planned to focus on better modelling of the physical properties of blood vessels and blood, as well as increasing the numbers of contributing factors.

CONCLUSION

This study investigated the effect of pathological blood vessels conditions like vasospasm, vasodilation, and haemorrhage on transcranial duplex ultrasonography parameters under artificial blood flow conditions. The most sensitive parameter for blood vessels condition changes was PSV — changes were observed in 100% of cases. The most insensitive parameters were TAPV, and MDV — changes were observed in 83% of cases. The results indicated that transcranial duplex ultrasonography has the potential to identify vasospasm, vasodilation, and haemorrhage in brain blood vessels by PSV values.

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TRANSKRANIĀLĀS DUPLEKSSONOGRĀFIJAS MĒRĪJUMI ASINSVADU STĀVOKĻA NOTEIKŠANAI

Zinātniski preklīniska pētnieciska darba mērķis bija izpētīt, kā transkraniālās duplekssonogrāfijas mērījumu rezultāti ir atkarīgi no asinsvadu stāvokļiem (vazospazms, vazodilatācija un asinsizplūdums) mākslīgās asinsrites apstākļos. Darba gaitā tika aplūkota transkraniālās duplekssonogrāfijas metode un fantomu izgatavošana. Tika aprakstītas izmantotās metodes un iegūtie rezultāti. Mērījumi tika veikti, izmantojot komerciāli pieejamu sonogrāfu un mākslīgās asinsrites aparātu, ūdens fantomu un 32% glicerīna šķīdumu ar kukurūzas cieti. Darba gaitā tika novērots, ka mākslīgās asinsrites apstākļos asinsvadu stāvoklis ietekmē asins plūsmas ātrumu — visjutīgākais pret asinsvadu izmaiņām ir asins plūsmas *PSV* (*Peak Systolic Velocity*) sistoliskā ātruma parametrs, kura izmaiņas tika novērotas 100% gadījumu, vismazāk jutīgais — MDV (*Minimum Diastolic Velocity*) parametrs, kura izmaiņas tika novērotas tikai 67% gadījumu.