European Conferences on Biomedical Optics 2021 (ECBO) © OSA-SPIE 2021

Dynamics of Cerebral Cortex Blood Flow and Tissue Abnormalities induced by Acute Respiratory Disorders

G.A. Piavchenko[*1,2], V.V. Dremin[2,3], I.O. Kozlov[2], D.D. Stavtsev[2], S.L. Kuznetsov[1], A.V. Dunaev[2], and I.V. Meglinski[1,3,4]

[1]*Department of Histology, Cytology and Embryology, First Moscow State Medical University named after I.M. Sechenov, Moscow, Russia*
[2]*Laboratory of Cell Physiology and Pathology, Orel State University named after I.S. Turgenev, Orel, Russia*
[3]*College of Engineering and Physical Sciences, Aston University, Birmingham, UK*
[4]*Opto-Electronics and Measurement Techniques, University of Oulu, Oulu, Finland*
**Correspondence: gennadii.piavchenko@yandex.ru*

Abstract: Understanding of acute respiratory pathology is critically important. We assess dynamics of cerebral cortex blood flow and tissue changes at the pathology in rats. Rapid blood flow centralization and irreversible brain tissue lesions are observed.

1. Introduction

Acute respiratory disorders are responsible for many critical states with a high mortality rate. They are treated in intensive care units of hospitals [1]. The main reasons of death in COVID-19 are definitely the respiratory system pathologies, both acute and chronic [2]. With the growth of pandemic situation, it is really important to understand the fundamental mechanisms of these pathologies development. Laser speckle contrast imaging becomes widespread for non-invasive blood flow imaging in brain *in vivo* [3]. Our research focuses on cerebral cortex blood flow dynamics and structural changes in brain tissue after modelling of the acute respiration impair in rats.

2. Materials and Methods

Male Wistar rats (2 months, 170 g, n=6) were introduced into the experiment after 2-weeks quarantine. The animals were anaesthetized with Zoletil drug (25 mg/kg, Vibrac, France) for inserting a PM-60 polymer catheter (SciCat, Russia, d_{ext}=0.8 mm, d_{int}=0.4 mm) into right external jugular vein. After that, the rats were placed in our own patented stereotaxic apparatus [4] and prepared for the trans-cranial laser speckle analysis with in-house built system that contained DCC3260M (Thorlabs, Inc., USA) with 1936×1216 pixels and 5.86-pixel size and 20 mW laser source with 785 nm wavelength (Thorlabs, Inc., USA) with diffuser for uniform illumination at the area of interest. For light collection, we used camera lens MVL25TM23 (Thorlabs, Inc., USA). Speckle contrast is associated with the movement of scattering particles inside the tissue and is in the range from 0 to 1. Also, speckle contrast is inversely proportional to the intensity of blood flow. After start of the recording, we provoked an acute respiration impair by inserting a drugs combination (propofol 0.3 ml and cisatracurium 0.5 ml) through the catheter for an immediate spasm of respiratory muscles. We recorded the data within 15 minutes to assess the blood flow dynamics in the cerebral cortex. Then we took the brain to evaluate of the signs of acute brain ischemia. The brain was placed into neutral formalin solution, embedded in paraffin for slicing and preparing of the histological specimens (5 μm tissue sections) further stained with methylene blue solution through the standard protocols. The results were analyzed with OriginPro (OriginLab Corp., USA) and MATLAB software. For the statistical analysis, several zones with different types of vessels had been initially selected: large sinuses and small vessels, predominantly of microcirculatory bed. All the manipulations with the animals were approved by the ethical committee of Orel State University named after I.S. Turgenev.

3. Results and Conclusions

We have found that mean speckle contrast increases in time. This growth is not linear – for 30 seconds it stays steady, then during the next minute increases rapidly, but by a point of 1.5 minutes the acceleration slows down varying in the blood vessels of different size (Fig. 1A-E).

To understand blood flow dynamics, we subdivide the vessels in accordance to its caliber (size). Further you can see marked specific areas of the vessels signed as small (vessels of microcirculation), medium (veins of medium size) and large (venous sinus) vessels (Fig. 1F). The results in the Fig. 2G show that the mean speckle contrast increases in time faster for the medium and small vessels. Meanwhile in large venous sinus it reaches the contrast values of the other vessels only 10 minutes after breathing stops, and at the point of 1.5 minute after the start this value is almost 1.5-2 time less than in small and medium vessels.

In histological specimens there are signs of acute hypoxia: a lot of wrinkled pycnotic neurons and vascular edema, necrobiosis of some neurons (Fig. 1H) comparing with a normal cerebral cortex section (Fig. 1I).

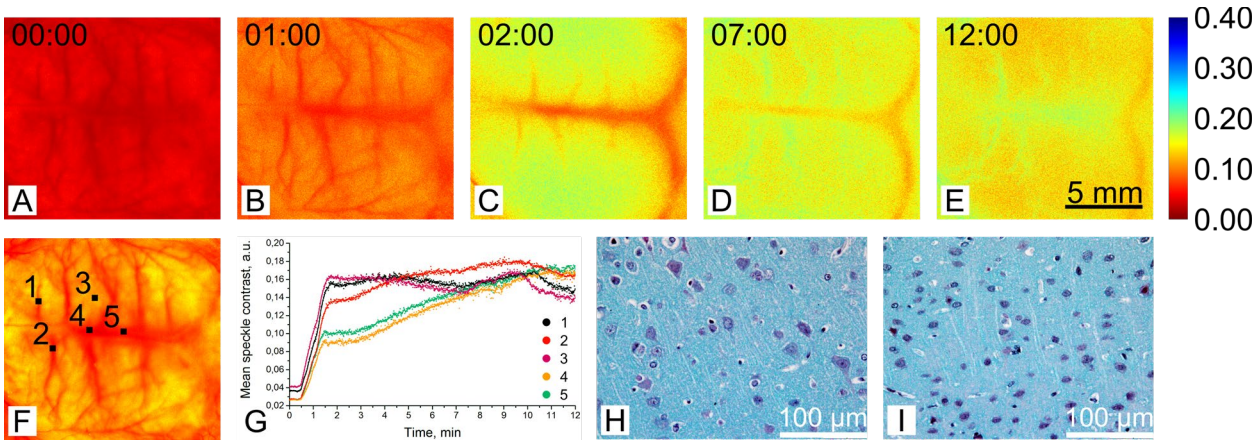

Fig. 1. Blood flow dynamics in time: (A) the baseline, (B) 1 minute after the respiratory impair, (C) 2 minutes, (D) 7 minutes and (E) 12 minutes. (F) Regions for an area estimation in respiratory and blood circulation impair: 1 and 2 – veins of medium size, 3 – vessels of microcirculation bed, 4 and 5 – venous sinus (large blood flow area) and (G) – dynamics of mean speckle contrast in time for selected areas. Brain cerebral cortex stained with methylene blue: (H) intact animals and (I) rats after acute respiratory impair.

Thus, during half of the minute only the blood circulation stays compensated due to the oxygen supply in the cerebral cortex vessels. Then, after a very short time there is a strong decompensation process occurring because of a growing oxygen deficiency. As a result, the body makes efforts to compensate the growing ischemia by an oxygen saving through the generalization of blood supply. This process tries to balance the lack of O_2 by decreasing the blood flow in small vessels with a priority for large sinuses. It helps to prolongate the period when the organism "fights for the life" in probably the most sensitive to O_2 deficiency cells, namely neurons.

After brain death caused by the acute impair of respiration, we mention signs of serious cellular and tissue degeneration. That proves our hypothesis that a fast-growing ischemia occurs in brain cortex after several minutes without an oxygen supply. Even though in our previous report [5] we have found that a heart arrest is more acute than a respiratory arrest, we note here that rat organism may recover cerebral blood flow after the acute respiration impair for only 1-2 minutes. After that, there are distinct and irreversible organic lesions that are found in the histological specimens.

4. Acknowledgements

Viktor Dremin kindly acknowledges personal support from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 839888. Andrey Dunaev and Igor Meglinski acknowledge funding from the Academy of Finland (grant No. 326204).

5. References

[1] Huang, X., Zhang, R., Fan, G. *et al.,* "Incidence and outcomes of acute respiratory distress syndrome in intensive care units of mainland China: a multicentre prospective longitudinal study," Crit Care **24,** 515 (2020).

[2] Conditions contributing to deaths involving coronavirus disease 2019 (COVID-19). National Center for Health Statistics Website, USA. Source: https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#Comorbidities.

[3] Kalchenko, V., Israeli, D., Kuznetsov, Y.L., *et al.,* "A simple approach for non-invasive transcranial optical vascular imaging (nTOVI)," J. Biophoton. **8**, 897 – 901 (2015).

[4] Gryadunov, I.M., Piavchenko, G.A., Kozlov, I.O., Seryogina, E.S., Kuznetsov, S.L. Laboratory stereotaxis device. Official Bulletin "Inventions. Useful models," Moscow: FIPS, 2020, No. 28. Source: https://www1.fips.ru/ofpstorage/Doc/IZPM/RUNWU1/000/000/000/200/025/%D0%9F%D0%9C-00200025-00001/document.pdf.

[5] Piavchenko, G.A., Seryogina, E.S., Kandurova, K. Yu., *et al.,* "Brain metabolism changes in cases of impaired breathing or blood circulation in rodents evaluated by real time optical spectroscopy methods," in: *Optical Biopsy XVIII: Toward Real-Time Spectroscopic Imaging and Diagnosis*, R.R. Alfano, S.G. Demos, A.B. Seddon, eds., *Proc. SPIE*, Vol.**11234**, 112341E (2020).