Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Can efficient stimulation of myogenic microcirculatory oscillations by transient ischemia predict low incidence of COVID-19 infection?

Oscillations in the microcirculation, known as flowmotion, are a well-recognized characteristic of cutaneous blood flow (Rossi et al., 2006). Very recently, we demonstrated that skin flowmotion can be monitored distinctly and precisely using the Flow Mediated Skin Fluorescence (FMSF) technique (Gebicki et al., 2020a). The FMSF technique appears to be uniquely suited to the analysis of basal flowmotion and its hypoxia response, and may be used for characterization of microcirculatory status. The FMSF technique is based on monitoring the intensity of NADH fluorescence from skin tissue on the forearm as a function of time, in response to blocking and releasing blood flow. Full details of the FMSF technique are available elsewhere (Katarzynska et al., 2019). Measurements are performed using the AngioExpert, a diagnostic device constructed by Angionica Ltd. Two different periods of oscillations can be distinguished in the FMSF signal: basal oscillations at rest and flowmotion during the reperfusion stage. Analysis of flowmotion on the reperfusion line following post-occlusive reactive hyperemia (PORH) allows for quantitative assessment of the patient's reaction to hypoxia caused by transient ischemia. The best measure of oscillations during the reperfusion stage is the Hypoxia Sensitivity (HS) parameter, which covers the intensity of flowmotion related to myogenic oscillations (0.052–0.15 Hz). Since myogenic oscillations are predominantly stimulated on the reperfusion line following transient ischemia, the HS parameter seems to be particularly well-suited for quantitative characterization of the microcirculatory response to hypoxia.

Based on FMSF studies involving several hundred patients, we have identified four ranges of HS values, describing distinguishable levels of microvascular function (very low, low, moderate and high), as shown in Fig. 1. Additionally, a correlation was found between the HS parameter and blood pressure.

In a recent communication, we proposed that the microcirculatory response to hypoxia could be a prognostic factor for COVID-19 (Gebicki et al., 2020b). This was supported by extensive literature linking innate immunity directly to hypoxia (Colgan et al., 2020). We have recently observed that several individuals who contracted COVID-19 and for whom the measured HS parameter was relatively high (above 70) passed the infection with mild symptoms. The measured HS parameter for diabetes patients with chronic foot ulcer is very low (below 8) and the prognosis for COVID-19 infection is indeed poor. Now, we report the results of a limited preliminary study that suggests the HS parameter can be used to predict low incidence of COVID-19. The case report concerns four members of a household (A, B, C, D), without any associated medical problems, one of whom (A) was infected with the SARS-CoV-2 virus. The characteristics of the household members are presented in Table 1 and FMSF traces for A and B are presented in Fig. 2.

The FMSF trace recorded for the infected family member before infection shows weak microcirculatory oscillations on the reperfusion line (Fig. 2A). The HS value of 39.6 seems to predict moderate symptoms.

The non-infected family members (B, C and D) are characterized by high values for the HS parameter and low blood pressure. We tentatively propose that both the efficient stimulation of myogenic oscillations by transient ischemia (high value of the HS parameter) and low blood pressure predispose the patient to low incidence of COVID-19 infection. The arguments supporting this proposition are presented below.

As COVID-19 spreads, there have been numerous situations in which one member of a household is infected and has contact with the others. Despite precautions, it is very difficult to avoid exposing other members of the household to the virus. However, numerous cases have shown that the infection of one person does not necessarily result in transmission to all members of the household (Grijalva et al., 2020). Clearly, some individuals are resistant to contracting the infection, although the current state of knowledge is insufficient to explain why.

The strong correlation between the HS parameter and blood pressure presented in Fig. 1b and c is intriguing. A recently published report by Whelton et al. shows a strong association between systolic blood pressure (SBP) and coronary artery calcium, with rising incidence of atherosclerotic cardiovascular disease (ASCVD) in patients without other risk factors (Whelton et al., 2020). At SBP levels as low as 90 mm Hg, there appears to be a continuous increase in the presence of coronary artery calcium, and the risk of incident ASCVD rises with SBP levels. This poses the question of what blood pressure should be regarded as normal. Given the correlation between SBP above 90 mm Hg and artery stiffness, it is not surprising that the HS parameter representing the stimulation of myogenic oscillations by transient hypoxia is strongly blood pressure dependent and reaches the highest values at very low blood pressure levels.

There are numerous reports indicating the protective effects of HIF-1α against epithelial injury via the hypoxic preconditioning mechanism (Olson et al., 2011; Serebrovska et al., 2020). Such protection can minimize the loss of epithelial barrier integrity by oxidative stress. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane serine protease 2 (TMPRSS2) when it enters the host cell. It is postulated that HIF-1α exerts an inhibitory effect on ACE2, thereby controlling the entry of the virus into pulmonary epithelium. This assumption is supported by the decreased severity of infection by SARS-CoV-2 under hypoxic conditions at high altitudes (Arias-Reyes et al., 2020). It is likely that the high value of the HS parameter reflects the efficient stabilization of HIF-1α under transient hypoxia. The response to hypoxic stress due to the presence of a virus should result in stabilization of HIF-1α. As HIF-1α participates in regulation of immune cells the individuals with a remarkable response to hypoxia (high values of the HS parameter) might have an elevated level

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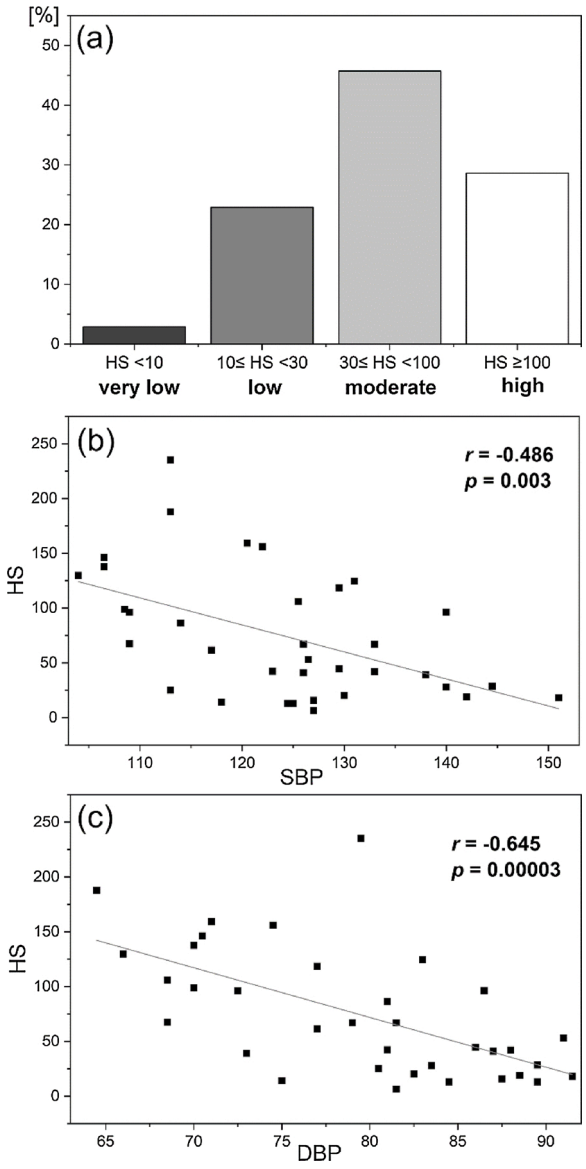

Fig. 1. (a) Distribution of the HS parameter in a group of healthy middle-aged individuals, n = 35 (male-22, female-13), mean age 38.5 (30–50 y.). Correlation between the HS parameter and systolic (SBP) (b) and diastolic (DBP) (c) blood pressure for this group.

Table 1
Characteristics of the household members.

Household members	Infection severity	Sex	Age [years]	Blood pressure [mm Hg]		HS
				SBP	DBP	
A	moderate[a,b]	M	50	114	80	39.6
B	non-infected[c]	F	49	108	64	117.5
C	non-infected[c]	F	19	102	61	109.1
D	non-infected[c]	M	14	98	58	186.2

[a] High temperature, severe headache, loss of smell and taste, fatigue, symptoms duration – 12 days.
[b, c] IgG and IgM antibody test: positive (b), negative (c).

of CD4 T-cells reactive against the spike glycoprotein of SARS-CoV-2 (Braun et al., 2020; Taylor et al., 2016).

As shown in Fig. 1, the HS parameter correlates with the blood pressure and both these variables seem to be regulated by HIF-1α in

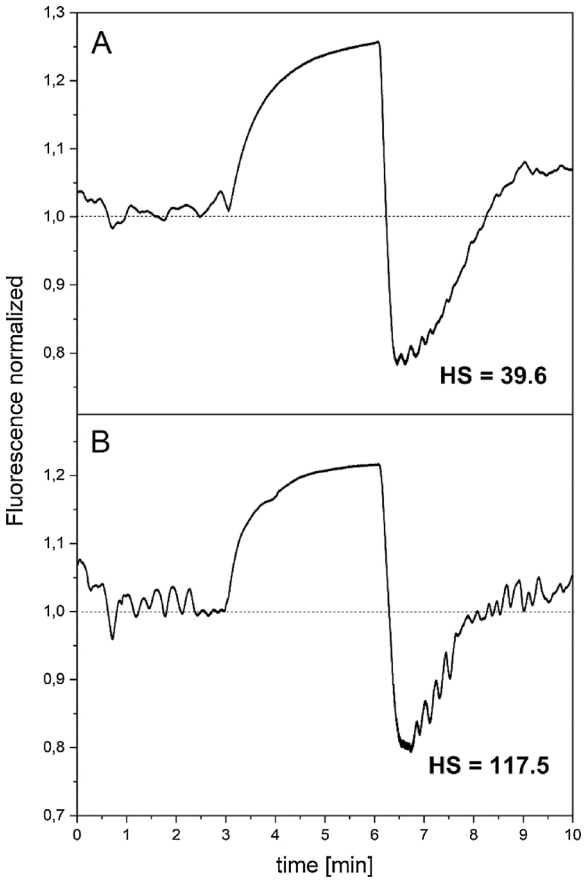

Fig. 2. FMSF traces for household members (A and B) with the measured HS parameters.

vascular smooth muscle cells (Cowburn et al., 2013; Huang et al., 2013). Therefore, it is not surprising that hypertension has been recognized as a serious cause of the severity and mortality of COVID-19. This preliminary observation deserves careful verification in further studies. If confirmed, it could be of valuable assistance in managing the COVID-19 pandemic.

As hypoxia is associated with the development of many diseases and disorders, it may more generally be concluded that the body's normal reaction to oxygen deficiency via stimulation of myogenic microcirculatory oscillations can minimize detrimental hypoxic effects on tissues. The HS parameter measured with FMSF technique seems to offer a simple and quite universal estimate of microcirculatory status.

Declaration of Competing Interest

JG and AM are inventors of the patents protecting the use of FMSF technology.

References

Arias-Reyes, C., Zubieta-DeUrioste, N., Poma-Machicao, L., Aliaga-Raduan, F., Carvajal-Rodriguez, F., Dutschmann, M., Schneider-Gasser, E.M., Zubieta-Calleja, G., Soliz, J., 2020. Does the pathogenesis of SARS-CoV-2 virus decrease at high-altitude? Respir. Physiol. Neurobiol. 277, 103443. https://doi.org/10.1016/j.resp.2020.103443.

Braun, J., Loyal, L., Frentsch, M., Wendisch, D., Georg, P., Kurth, F., Hippenstiel, S., Dingeldey, M., Kruse, B., Fauchere, F., Baysal, E., Mangold, M., Henze, L., Lauster, R., Mall, M.A., Beyer, K., Röhmel, J., Voigt, S., Schmitz, J., Miltenyi, S., Demuth, I., Müller, M.A., Hocke, A., Witzenrath, M., Suttorp, N., Kern, F., Reimer, U., Wenschuh, H., Drosten, C., Corman, V.M., Giesecke-Thiel, C., Sander, L. E., Thiel, A., 2020. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. Nature 587, 270–274. https://doi.org/10.1038/s41586-020-2598-9.

Colgan, S.P., Furuta, G.T., Taylor, C.T., 2020. Hypoxia and innate immunity: keeping up with the HIFsters. Annu. Rev. Immunol. 38, 341–363. https://doi.org/10.1146/annurev-immunol-100819-121537.

Cowburn, A.S., Takeda, N., Boutin, A.T., Kim, J.W., Sterling, J.C., Nakasaki, M., Southwood, M., Goldrath, A.W., Jamora, C., Nizet, V., Chilvers, E.R., Johnson, R.S., 2013. HIF isoforms in the skin differentially regulate systemic arterial pressure. Proc. Natl. Acad. Sci. U. S. A. 110, 17570–17575. https://doi.org/10.1073/pnas.1306942110.

Gebicki, J., Katarzynska, J., Cholewinski, T., Sieron, L., Marcinek, A., 2020a. Flowmotion monitored by flow mediated skin fluorescence (FMSF): a tool for characterization of microcirculatory status. Front. Physiol. 11, 702. https://doi.org/10.3389/FPHYS.2020.00702.

Gebicki, J., Katarzynska, J., Marcinek, A., 2020b. Can the microcirculatory response to hypoxia be a prognostic factor for Covid-19? Respir. Physiol. Neurobiol. 280, 103478. https://doi.org/10.1016/j.resp.2020.103478.

Grijalva, C.G., Rolfes, M.A., Zhu, Y., McLean, H.Q., Hanson, K.E., Belongia, E.A., Halasa, N.B., Kim, A., Reed, C., Fry, A.M., Talbot, H.K., 2020. Transmission of SARS-COV-2 infections in households — Tennessee and Wisconsin, April–september 2020. MMWR Morb. Mortal. Wkly. Rep. 69, 1631–1634. https://doi.org/10.15585/mmwr.mm6944e1.

Huang, Y., Di Lorenzo, A., Jiang, W., Cantalupo, A., Sessa, W.C., Giordano, F.J., 2013. Hypoxia-inducible factor-1α in vascular smooth muscle regulates blood pressure homeostasis through a peroxisome proliferator-activated receptor-γ-angiotensin II receptor type 1 axis. Hypertension (Dallas, Tex. 1979) 62, 634–640. https://doi.org/10.1161/HYPERTENSIONAHA.111.00160.

Katarzynska, J., Lipinski, Z., Cholewinski, T., Piotrowski, L., Dworzynski, W., Urbaniak, M., Borkowska, A., Cypryk, K., Purgal, R., Marcinek, A., Gebicki, J., 2019. Non-invasive evaluation of microcirculation and metabolic regulation using flow mediated skin fluorescence (FMSF): technical aspects and methodology. Rev. Sci. Instrum. 90, 104104. https://doi.org/10.1063/1.5092218.

Olson, N., Hristova, M., Heintz, N.H., Lounsbury, K.M., van der Vliet, A., 2011. Activation of hypoxia-inducible factor-1 protects airway epithelium against oxidant-induced barrier dysfunction. Am. J. Physiol. Cell. Mol. Physiol. 301, L993–L1002. https://doi.org/10.1152/ajplung.00250.2011.

Rossi, M., Carpi, A., Galetta, F., Franzoni, F., Santoro, G., 2006. The investigation of skin blood flowmotion: a new approach to study the microcirculatory impairment in vascular diseases? Biomed. Pharmacother. 60, 437–442. https://doi.org/10.1016/j.biopha.2006.07.012.

Serebrovska, Z.O., Chong, E.Y., Serebrovska, T.V., Tumanovska, L.V., Xi, L., 2020. Hypoxia, HIF-1α, and COVID-19: from pathogenic factors to potential therapeutic targets. Acta Pharmacol. Sin. 41, 1539–1546. https://doi.org/10.1038/s41401-020-00554-8.

Taylor, C.T., Doherty, G., Fallon, P.G., Cummins, E.P., 2016. Hypoxia-dependent regulation of inflammatory pathways in immune cells. J. Clin. Invest. 126, 3716–3724. https://doi.org/10.1172/JCI84433.

Whelton, S.P., McEvoy, J.W., Shaw, L., Psaty, B.M., Lima, J.A.C., Budoff, M., Nasir, K., Szklo, M., Blumenthal, R.S., Blaha, M.J., 2020. Association of normal systolic blood pressure level with cardiovascular disease in the absence of risk factors. JAMA Cardiol. 5, 1011–1018. https://doi.org/10.1001/jamacardio.2020.1731.

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