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RESEARCH LETTER

Effect of Psychological Stress on Microcirculation Oscillations: Diagnostic Aspects

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It has long been recognized that psychological stress contributes to heart disease. Prolonged psychological stress is now seen as an important risk factor for the entire vascular system.[1] However, there have been relatively few studies on the effects of psychological stress on the microcirculation. Psychological stress is associated with increased levels of norepinephrine in the circulation, which can cause microvascular vasoconstriction. Using laser Doppler flowmetry, healthy individuals with self-reported high levels of daily psychological stress have been found to show greater norepinephrine-induced vasoconstriction compared with healthy individuals with low stress.[2] Therefore, in this study, we consider microvascular flow perturbation caused by psychological stress as a reliable diagnostic method of stress assessment.

There has recently been tremendous progress in the development of wearable technologies for monitoring stress. The majority of wearable stress devices are based on continuous monitoring of the heart rate. An increased heart rate is a normal physiological response to acute emotional stress or physical exercise. It seems unlikely that such responses will directly translate to negative consequences caused by stress. More recently, wearable stress devices have been developed based on heart rate variability (HRV).[3] This approach seems more rational for the assessment of vascular consequences caused by stress, particularly in the healthy population. However, the measured HRV can be attenuated in individuals suffering from diseases affecting the vascular system, such as diabetes, CVD, hypercholesterolemia, or hypertension. Therefore, HRV may not be a reliable measure of stress.

Very recently, we showed that chronic fatigue associated with post-COVID syndrome and transient fatigue caused by high-intensity exercise are comparable in terms of vascular effects.[4] The analysis of microcirculation oscillations detected at rest using the Flow Mediated Skin Fluorescence (FMSF) technique can be of particular use for monitoring physical stress related to strenuous exercise or post-infection fatigue. It is rational to assume that a similar methodology can be applied to assess the vascular consequences of psychological stress. This short contribution presents the effects of prolonged psychological stress on microcirculation oscillations monitored by the FMSF technique and discusses the diagnostic implications.

Measurements were performed using the AngioExpert, a device constructed by Angionica Ltd. The AngioExpert device uses the Flow Mediated Skin Fluorescence (FMSF) technique, which measures changes in the intensity of nicotinamide adenine dinucleotide (NADH) fluorescence from the skin on the forearm in response to blocking and releasing blood flow. The skin is the largest organ of the human body and is characterized by specific metabolism. The epidermal layer of the skin is not directly vascularized, and oxygen and nutrients are transported from the dermis by diffusion. Therefore, epidermal cell metabolism can be considered as a unique and sensitive marker of early dysfunction in vascular circulation and metabolic regulation.

Oscillations in the microcirculation, known as flowmotion, are a well-recognized characteristic of cutaneous blood flow. We have demonstrated that skin flowmotion can be monitored very distinctly and precisely using the FMSF technique.[5,6] Two different periods of oscillations can be distinguished in the FMSF signal: basal oscillations at rest and flowmotion during the reperfusion following post-occlusive reactive hyperemia (PORH). For the purposes of the present study, only flowmotion at rest will be analyzed. The blood flow oscillations in the low-frequency range (<0.15 Hz) fit into several periodic activities, classified as endothelial (<0.021 Hz), neurogenic (0.021–0.52 Hz), and myogenic (0.052–0.15 Hz). Two parameters characterizing flowmotion at rest will be used: FM, a parameter characterizing the intensity of oscillations in the low-frequency range (<0.15 Hz); NOI

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(Normoxia Oscillatory Index). The NOI parameter represents the contribution of endothelial and neurogenic oscillations relative to all oscillations detected at low-frequency intervals (<0.15 Hz).[4] Based on numerous FMSF measurements of patients affected by stress of various origins, it has been established that a low NOI value (<60%) indicates microcirculatory disorders caused by a stress factor, such as emotional stress, physical exhaustion, or post-infection stress, and may be reversible. Chronically low NOI values can lead to the development of serious vascular circulatory disorders.

Figure 1 presents exemplary FMSF baseline traces, showing pronounced microcirculation oscillations for a patient frequently monitored by the FMSF diagnostic technique. Segment (a) shows typical microcirculatory

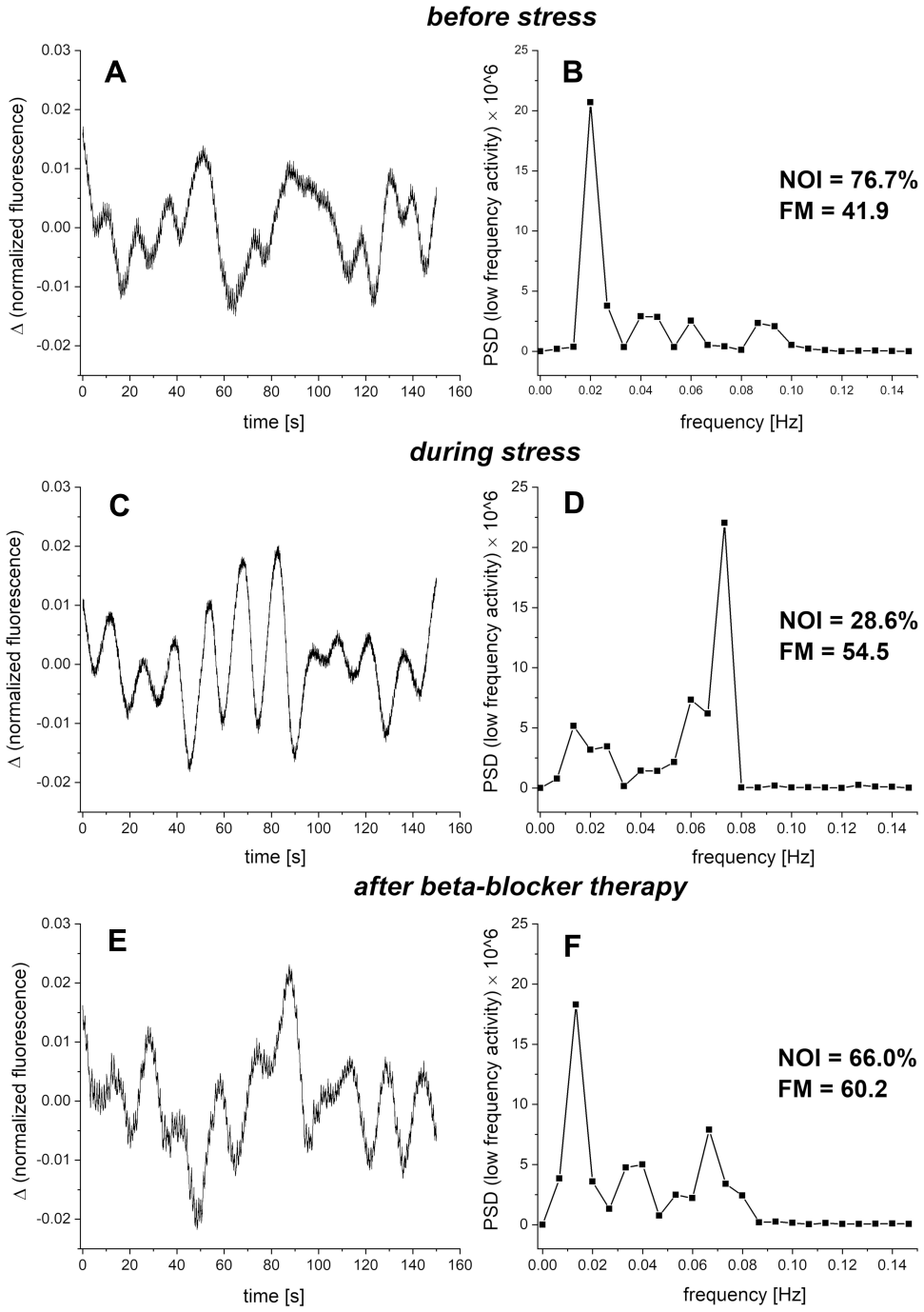

Figure 1 Exemplary FMSF baseline traces recorded for a prediabetes patient (male, age range 70–75 y). Changes in the fluorescence signal relative to the normalized baseline (left) and the corresponding Power Spectral Density (PSD) of the fluorescence signal in the intervals of endothelial (<0.021 Hz), neurogenic (0.021–0.052 Hz), and myogenic (0.052–0.15 Hz) activity (right): (**A** and **B**) – changes recorded before the appearance of psychological stress; (**C** and **D**) – changes observed under prolonged psychological stress; (**E** and **F**) – changes observed after a week of therapy with a beta-blocker (nebivolol at a daily dose of 1.25 mg).

oscillations in the low-frequency range, measured for the patient in the state of relaxation without any self-declared stress. Segment (b) shows the corresponding Power Spectral Density (PSD) of the fluorescence signal. Microcirculation oscillations are dominated by the endothelial component (<0.021 Hz) and the measured NOI value is 76.7%. The measurements for this patient under self-declared prolonged emotional stress principally caused by a traumatic event are shown in segments (c) and (d). Microcirculation oscillations are dominated by the myogenic component (0.052–0.15 Hz) and the measured value of the NOI parameter is only 28.6%. The observed increase of myogenic activity in this case is evidently due to the ischemic response caused by microcirculation vasoconstriction. Similar activation of myogenic microcirculatory oscillations is seen on the reperfusion line during the FMSF-PORH test.[5,6] The patient contacted a medical doctor, who recommended a very low dose of beta-blocker (nebivolol at a daily dose of 1.25 mg). The FMSF measurement performed on the seventh day after initiation of beta-blocker therapy and the results are presented in segments (e) and (f). As can be seen, the measured NOI parameter increased to 66.0%, a level typical for unstressed individuals (NOI > 60%). This observation correlates with the patient's subjective report of feeling less stressed with decreased anxiety. The patient gave written consent to use these results for publication purposes.

The results presented in Figure 1 clearly indicate that the NOI parameter is suitable for evaluation of psychological stress, and that a low dose of beta-blocker can be recommended for mild psychological stress. It has been suggested previously that beta-adrenergic blockade attenuates negative, high arousal emotions in response to a psychosocial stressor.[7]

Figure 2 compares the NOI and FM parameters for two groups of patients: group A – healthy middle-aged individuals; group B – diabetes type 2 patients. Brief characteristics of the studied population is given in the caption of Figure 2. The patients in groups A and B had not suffered from COVID-19 infection and were physically relaxed before the FMSF measurements. Unsurprisingly, the FM parameter was lower for group B than group A. This difference in the intensity of low frequency microcirculatory oscillations is due to the differences in the age and health status of the

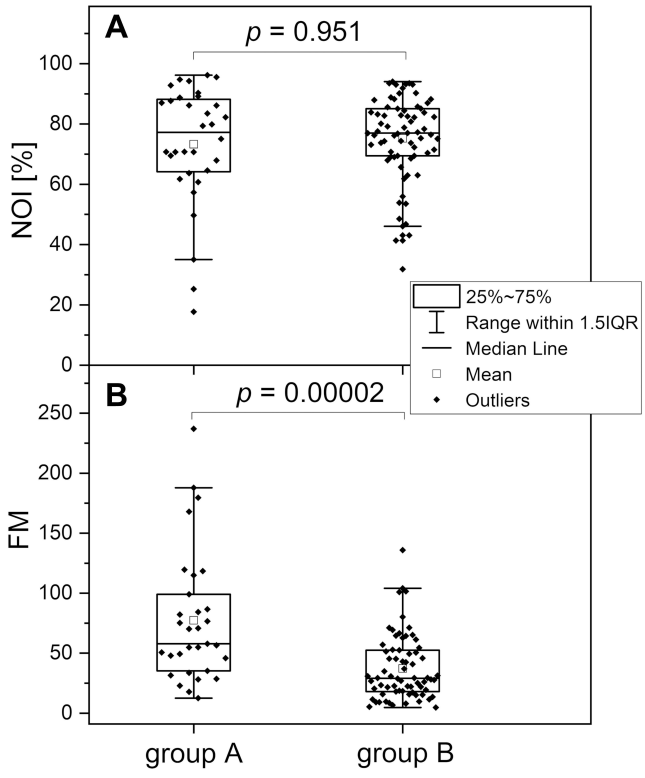

Figure 2 Comparison of the NOI (**A**) and FM (**B**) parameters in groups A and B (group A healthy middle-aged individuals, n=32, 19m, 13f, mean age 37.8 (30–50 y)); (group B diabetes type 2 patients, n=70, 38m, 32f, mean age 63.1 (45–80y.)). Differences between the parameters of the compared groups were considered statistically significant when p<0.05. The p-values were calculated from the results of the Mann–Whitney test.

members of the studied groups.[5,6] However, no difference was noted in the NOI values for the two groups. This suggests that the NOI parameter can be used as an universal measure of psychological stress, regardless of age and health status (diabetes). Five of the 32 individuals in group A had an NOI value of less than 60%. In group B, a similar proportion (9 out of 70) also had an NOI parameter lower than 60%. This means that about 16% of the individuals in group A and 13% in group B were affected by a stress predominantly of psychological origin, which was visible as a disturbance in their microcirculatory oscillations. The NOI values seem to be particularly low in pre-menopausal females.

The results of this study and the results presented in reference[4] for stress due to physical exhaustion and viral infection suggest that the NOI parameter can be used to evaluate stress of any origin. However, some distinctive differences were noticed. Physiological stress causes an evident relative increase in myogenic oscillations at relatively stable intensity of low frequency microcirculatory oscillations, as measured by the FM parameter. The stress caused by high-intensity exercise or post-COVID syndrome was manifested predominantly by a substantial decrease in endothelial and neurogenic oscillations at relatively stable intensity of myogenic oscillations, resulting in a decrease in the FM parameter. The use of the Flow Mediated Skin Fluorescence (FMSF) technique to assess the vascular consequences of psychological stress is particularly attractive due to the non-invasive nature of the FMSF technique and the possible adaptation of this methodology for use in wearable devices.

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Disclosure

JK is employed by Angionica Ltd. JG and AM are inventors of the patents protecting the use of FMSF technology issued to Angionica Ltd. The authors report no other conflicts of interest in this work.

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