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Wearable non-invasive monitors of diabetes and hypoxia through continuous analysis of sweat

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ABSTRACT

We present here wearable devices for continuous monitoring of diabetes and hypoxia based on continuous analysis of sweat. To induce sweating the clinically relevant procedure (pilocarpine electrophoresis) is used. Being a sufficient requirement for diagnostics, positive correlations in variation rates between glucose and lactate concentrations in sweat and the corresponding values in blood are shown. Continuous monitoring of human condition is possible only with the use of flow-through wearable devices providing a delivery of sweat to the biosensor almost immediately after secretion. Evaluating blood glucose through continuous sweat analysis upon glucose tolerance test, we clearly show that diabetics can actually be monitored reliably via non-invasive approach.

Great interest to wearable devices is illustrated by an avalanche of papers: a search through Web of Science returns more than 93 000 citations. Of major importance among them are sensor systems allowing continuous evaluation of key blood metabolites.

Non-invasive methods, which exclude not only injury to blood vessels, but also damage to the skin surface, are preferred for diagnostics: such methods are painless and avoid potential infection and trauma to patients. However, even for blood glucose the problem for its non-invasive evaluation cannot be considered as solved. Physical methods were not successful, particularly, near-IR spectroscopy could not provide the required sensitivity and selectivity [1–4]. The attempts to deliver interstitial fluid to the skin surface by reverse iontophoresis for non-invasive glucose monitoring [5,6] was also unsuccessful in commercialized devices.

Non-invasively collected sweat has already found use in clinical diagnostics: measuring its conductivity it is possible to diagnose cystic fibrosis (mucoviscidosis) [7–9]. It is important, that for sweat sampling the clinically relevant procedure (sweat gland activation through pilocarpine electrophoresis) [10,11] is generally accepted. The metabolite content in such samples is known to be independent of the sweating rate [12].

1. Sweat validation for monitoring of hypoxia and diabetes

The most important low-molecular weight metabolites, which levels have to be monitored throughout the day, are undoubtedly glucose and lactate. Glucose concentration in blood is the key parameter for diabetic patients: maintaining it at an appropriate level allows complications of this disease to be postponed. Being one of the leading causes of death in the world, diabetes is dangerous because of its complications: cardiovascular diseases, blindness, risk of amputation, kidney failure, etc. As for L-lactate, being the product of glycolysis, anaerobic glucose metabolism, it is known as a marker of hypoxia [13,14]. Besides that, it allows to control training level of sportsmen, for example, calculating lactate anaerobic thresholds [15–17].

Sweat has been considered for non-invasive monitoring of diabetes and hypoxia. However, the attempts to predict blood glucose on the basis of sweat glucose concentration [18,19] were not successful. As for sweat lactate, the negative conclusion on its suitability for diagnostics [20] is accepted.

As mentioned, non-invasive methods exclude even damage to the skin surface, hence, for chemical analysis the only excreted liquids, like saliva, urine, sweat etc. – can be considered. Accordingly, non-invasive monitoring by means of (bio)sensors is often considered unreliable since none of such excreted liquids directly replicate the metabolite content of blood. We, however, note that the majority of existing long-term glucose monitors referred to as “low-invasive” require calibration, which involves a conventional blood probing with subsequent glucose detection in it. Hence, a sufficient requirement for non-invasive diagnostics would be a correlation in variation rates between metabolite concentrations in the excreted liquid and the corresponding values in blood.

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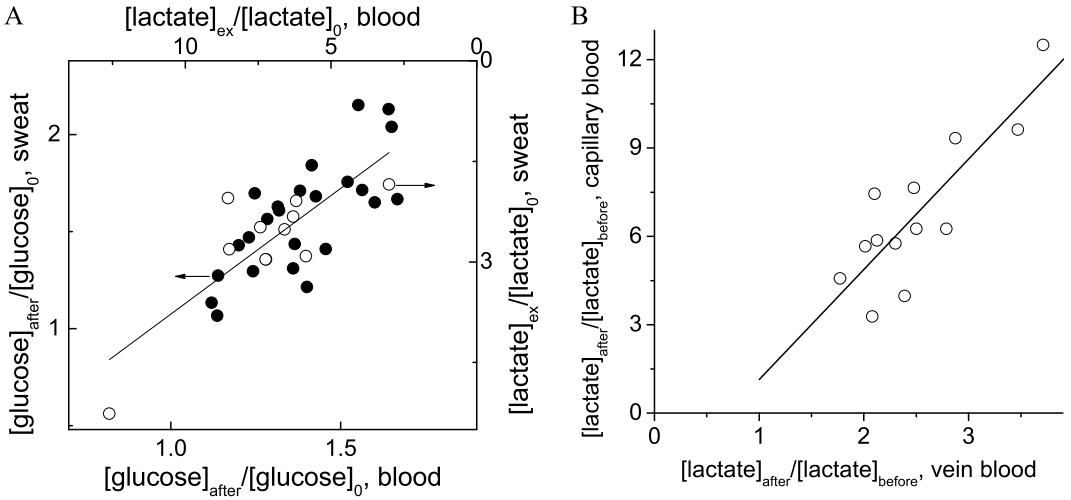

Fig. 1. Correlations between variation rates of metabolite content: (A) for glucose (○) and lactate (●) between sweat and capillary blood; (B) for lactate between venous blood and capillary blood.

We also note that despite blood is considered as a liquid with undoubted diagnostic potential, in different vessel systems its metabolite content is different. Recalculating our data obtained 10 years ago [21], we've found that even in terms of variation rates correlation between venous blood lactate and capillary blood lactate is characterized by Pearson correlation coefficient of 0.8, however, the regression line has a slope of 3.8 and an intercept of −2.6 (Fig. 1B).

Considering correlation in variation rates of glucose content between sweat and blood, it displays similar Pearson coefficient (0.75), however, the regression line is characterized by a slope of 1.3 and an intercept of −0.2 (Fig. 1A) [22], which is significantly better as compared to correlation between blood from different vessel systems (see Fig. 1B). Variation rates in lactate concentration correlate with the Pearson coefficient even above 0.8 [23], and the slope of the regression line and the intercept are, respectively, 0.32 and 0.4 (Fig. 1A). Hence, the observed correlation in variation rates of metabolite content between sweat and capillary blood is not worse, and in some cases is even better than the correlation between blood samples from different vessel systems. Accordingly, sweat is suitable for diagnostics concerning its ability to evaluate blood metabolite content.

The important question, however, is how often it is necessary to calibrate the wearable device operating through sweat analysis. Our preliminary estimations show that the ratio between blood and sweat metabolite glucose content for a particular subject remains unchanged for weeks [22]. Hence the estimated frequency of an invasive procedure (blood probing) upon the proposed non-invasive monitoring is once per weeks (or even a monthly probing).

2. Wearable flow-through biosensors for non-invasive monitoring

Wearable devices based on sweat analysis have been introduced by J. Wang [24]. The conception of the proposed 'tattoo' biosensor has been followed by other scientists proposing wearable devices for glucose [19,25–29] or/and lactate monitoring [28,30–33]. However, that the 'tattoo' based conception is not suitable for continuous monitoring of blood metabolites because the only first portion of sweat is able to reach successfully the sensor surface. Later excretes in such setup are mixed with previous portions returning mean sweat metabolite concentration instead of a current one and causing a significant delay in the response.

The only solution for real-time monitoring of sweat metabolites is first introduced by us [34] the flow-through biosensor. The concept is based on the Macroduct-type sweat collector substituting capillary at its outer surface by channel enzyme electrode. In such setup secreted sweat reaches the biosensor surface and wastes through the open outlet. The readout of the biosensor is in a good agreement with the sweat metabolite content measured independently by sampling it from the monitor outlet: Pearson correlation coefficient $r > 0.98$ [22,34].

The possibility of diabetes monitoring on the basis of flow-through biosensor through continuous analysis of sweat is shown in Fig. 2. As seen, the dynamics of blood glucose concentration is in a good accordance with the readout of the biosensor. No considerable delay in the dynamics of sweat glucose *vs* blood has been registered [22]. With this example, we thus clearly show that humans (diabetic patients, individuals subjected to glucose tolerance test, etc.) can actually be monitored reliably via non-invasive approach.

3. Conclusions

Concluding, the non-invasively collected sweat via clinically relevant procedure can be used for assessing the human condition, particularly for monitoring of diabetes and hypoxia. We note that continuous evaluation of blood metabolite concentrations on the basis of sweat analysis is possible only on the basis of flow-through biosensor

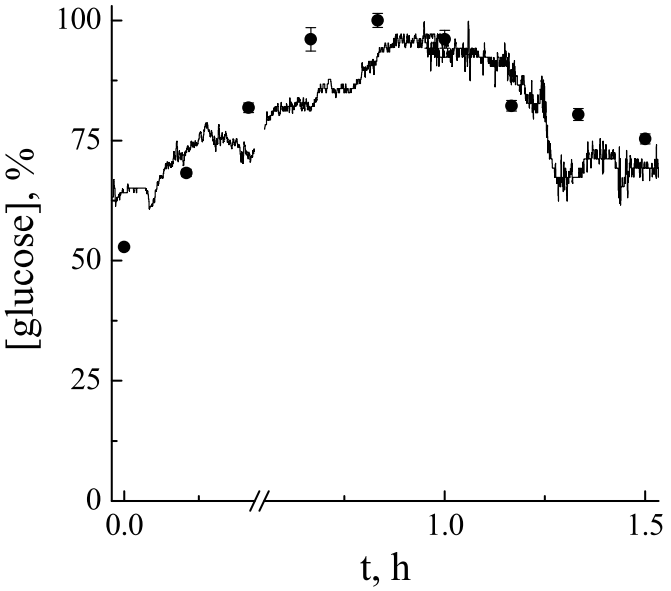

Fig. 2. Blood glucose levels (●) and the readings of the flow-through wearable monitor (solid) upon glucose tolerance test.

allowing sweat delivery to its surface as soon as possible after secretion.

For further clinical applications the required correlations in variation rates of metabolite content obtained for healthy subjects have to be confirmed in cases of the corresponding pathologies. Obviously, larger-scale validation of the proposed concept is strongly required.

Credit author statement

The manuscript was written through contributions of all authors.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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