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Commentary

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The sweat rate as a digital biomarker in clinical medicine beyond sports science

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Abstract
Sweating is an important physiological reaction and a clinical symptom in a variety of diseases. However, it remains underrated in clinical use. Gold standards to measure the sweat rate are neither continuous nor easily or lab-independently applicable. With the emergence of novel wearable devices, using the sweat rate as a digital biomarker shows promise for clinical monitoring and diagnostics. In this Commentary, we discuss the potential and importance of the sweat rate as a digital biomarker in clinical medicine beyond sports science.

Keywords: Wearables, sweat analysis, sweat rate, clinical sweat analysis, digital biomarkers

INTRODUCTION
Sweating is an important physiological reaction to maintain the body's thermoregulation during exposure to environmental heat stress or during rigorous exertion. This is one of the main reasons why the sweat rate assessment has been increasingly investigated in sports science and occupational health since the emergence of wearable sweat sensing. Reports from diseases such as the "Sudor Anglicus" in the 15th century, alongside common medical knowledge from oncology and infectious diseases, have shown that sweating has not only a thermo-regulatory function but it can be a symptom in clinical medicine as well[1-3]. Therefore, sweat analysis provides valuable information about health, disease, and even age[4,5]. Still, the

sweat rate remains underexplored and underrated in clinical medicine. However, with the emergence and continuous advancements of sweat analyzing wearables, sweat rate analysis holds the potential to become a clinically, broadly available digital biomarker. In this Comment, we introduce and discuss the sweat rate as a promising novel digital biomarker to monitor health and disease in clinical medicine beyond sports science.

THE SWEAT RATE PHYSIOLOGY

Basics

The human body houses approximately two to four million sweat glands[6,7]. Eccrine, apocrine, and apoeccrine sweat glands can be distinguished[8,9]. While eccrine sweat glands are responsible for the highest volume of sweat excretion[10], secretion of apocrine and apoeccrine glands can also influence the sweat composition at the skin surface[11]. During sweating, up to 2,426 J of heat per gram of evaporated sweat can be dissipated from the body[12]. Aiming to maintain thermoregulation, sweating is the most efficient way to dissipate heat from the body. Next to heat stress, sweat glands can be stimulated by emotional stress[13], mechanical vibration[14], eating spicy food (gustatory hyperhidrosis)[15], or chemical substances such as carbachol and local current[16].

Neurological control

Many thermosensitive neurons can be found in the preoptic area and the anterior hypothalamus[17]. To keep the body temperature constant, they initiate appropriate responses when detecting changes in body temperature[17]. Augmented local preoptic temperature or a rise in afferent impulses from the cutaneous and spinal thermoreceptors caused by elevated skin temperature can both result in increased sweating[17]. However, increased core body temperature stimulates the sweat rate nine times more efficiently than increased mean skin temperature[18-20].

Body map

Local sweat rates for the mid-front, sides, and mid-later back were found to be significantly higher in males compared to females[21]. In both sexes, the highest sweating was observed along the spine, whereas the sweat rate on the upper arm was lowest. Furthermore, total sweating on the back exceeded the total sweating of the chest.

For older males, gross sweat loss and regional sweat rates were significantly lower compared to the young[22]. During rest, significantly lower regional sweat rates at almost all body regions were observed, whereas, during exercise, a significant difference was found for the hands, legs, ankles, and feet[22].

Influencing variables

Environmental factors such as ambient temperature, air velocity, and radiant load, along with factors such as clothing and the level of physical activity, influence the sweating rate [Figure 1][23].

Heat acclimatization of five to eight days results in thermoregulatory adaptions such as increased sweat rate and earlier onset of sweating[24]. However, depending on humid or dry heat exposure, the adaptation of the eccrine sweat gland differs: the sweat rate in a hot-humid environment is greater than in a hot-dry environment[24]. In healthy unacclimatized men, a sweating capacity of maximally 1.5 liters per hour has been reported, whereas, in highly trained acclimatized soldiers, a sweat rate of two to three liters per hour was reached[25]. Sweat rates of one liter per hour occur frequently depending on factors like the environment or the intensity of exertion; however, sweat rates can vary considerably[26]. Not only heat acclimatization but also training can lead to an increase of sweat rates of 200 to 300 mL per hour[26].

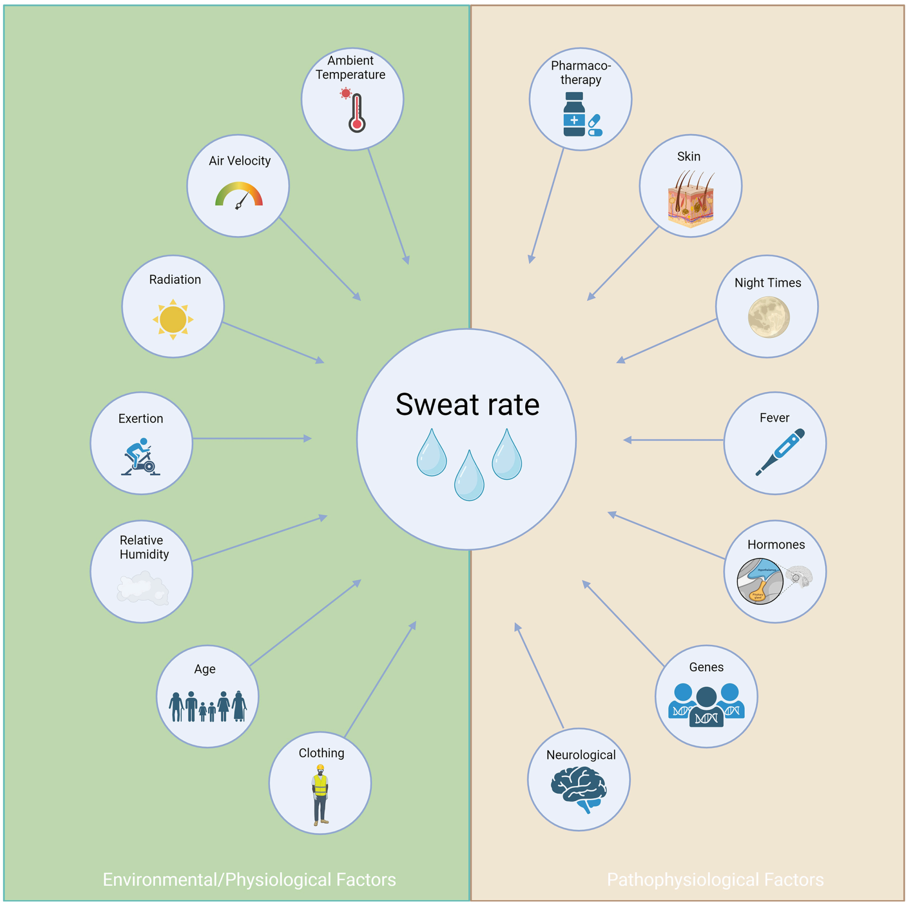

Figure 1. Factors influencing the sweat rate. Non-comprehensive overview of environmental/physiological and pathophysiological factors influencing the sweat rate, demonstrating the sweat rate as a digital biomarker going beyond sports science and occupational health. Created with BioRender.com.

WEARABLE SWEAT RATE ANALYSIS

Diagnostic instruments that rely on sweat samples collected using absorbent pads yield a wealth of information related to physiological status and athletic performance[27,28]. The protocols and the benchtop systems required for this purpose are, however, incompatible with real-time monitoring in the field. This is due to the bulk and expense of the hardware and the time and effort required for sample collection and preparation. Recent advances in flexible, hybrid electronics, soft microfluidics, and electrochemical sensors serve as foundations for emerging classes of skin-mounted systems for measuring the properties of sweat, each with features that overcome key limitations of conventional technologies[29-33].

The measurement of the sweat rate in skin-mounted systems occurs through microfluidic devices that capture the sweat directly from the glands [Figure 2]. The pressure that drives fluid flow arises from the action of the sweat glands themselves, assisted by capillary effects in the microchannels. The microfluidic system usually consists of a thin polymer layer [usually polydimethylsiloxane (PDMS)] embossed with appropriate relief geometry with a top-capping polymer layer [i.e., PDMS and polyethylene terephthalate (PET)] that serves as a seal[33]. The resulting overall thickness (usually smaller than 1 mm) and the addition of adhesive films enable intimate contact with the epidermis. Sweat rates strongly depend on the body location and the intensity of the exercise and may range from 39 to 614 $g \cdot h^{-1} \cdot m^{-2}$[22]. Therefore, microfluidic devices are typically designed to accommodate tens of uL. The inlet opening of a few mm in diameter

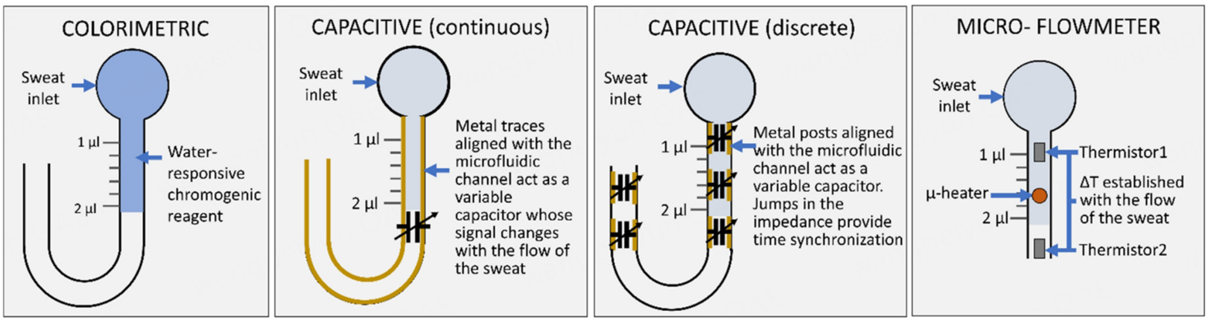

Figure 2. Overview of the main proposed approaches to measuring the sweat rate using wearable soft microfluidic sensors.

enables sweat collection of multiple glands, sometimes with the help of hydrophilic fillers for rapid sweat uptake[34]. The pressure that drives fluid flow arises from the action of the sweat glands themselves, assisted by capillary effects in the microchannels and the materials embedded within them. The measurement of the sweat rate can be implemented through various strategies that can be roughly categorized by transduction methods: (i) optical/visual; (ii) electrical (impedance, resistive). The former consists of fully passive devices (do not need a battery) in which the volume change is estimated visually or with the help of a camera[35-37]. More sophisticated designs offer quantitative information. They usually see the embedding of conductive traces or pads into the microfluidic channels. The flow of sweat induces changes in the electrical impedance. Initial designs suffered from the interdependence of the impedance on the volume and ionic concentration of the sweat, making the estimation of the rate difficult[34,38,39]. More recent designs have overcome this problem by (i) introducing differential measurements through two microfluid systems on the same patch (one for the ionic concentration and one for the rate)[40] and by (ii) patterning an array of pads along the channel to register discrete/digital changes of the impedance that enable time-volume synchronization independently from the ionic concentration[41]. It is worth mentioning that both methods require AC measurements to avoid the accumulation of ionic charge in the channels and the fouling of the impedance readout. This requirement complicates the circuit design of the wearable patch. While the previously mentioned devices rely on the indirect estimation of the rate via the measurement of the sweat volume and the passage time between some markers, another recent solution relies on the implementation of a flowmeter. This method involves reading the electrical resistance of two thermistors positioned on top of the microchannel and spaced out by a heater[42]. The flow of the sweat establishes a temperature change between the two thermistors whose dynamic response correlates with the flow rate. The simplicity of this strategy requires design optimization and intermittent operation to not incur high power consumption due to the heater. It is worth mentioning that all devices listed above are for single use: once the microfluidic is filled up, the device must be replaced by an empty one. Therefore, modular multi-layer designs are exploited to reuse the expensive layer that contains the electronic components and to dispose of the microfluidic layer that can be produced with biodegradable polymers[43]. An overview of typical specifications of wearable sweat rate sensors and a list of reported designs can be found in Table 1. Another major challenge deals with the production and collection of sweat that may be intermittent. Passive and active approaches rely on physical exercises and electro-/chemical stimulation, respectively. Iontophoresis is a widely used method of active sweat induction, allowing the acquisition of sweat samples while the body is sedentary. A current is generated under the skin surface by applying a voltage between the iontophoretic electrodes, allowing the agonist (e.g., pilocarpine molecules) to be delivered to the sweat gland at the anode and stimulating the secretion of sweat[33]. Such an approach has proved to be effective for the monitoring of chloride[44], ethanol[45], c-reactive protein[46], hormones[47], and glucose[44,48]. Other more innovative methods rely on optical infra-red imaging combined with skin temperature and environmental conditions to assess the activity of multiple sweat glands[49] or on the use of sweat-responsive covalent organic films for sweat pores

Table 1. Typical specifications of wearable sweat rate sensors

Device	Materials and design of μ-fluidics	Sweat rate measurement	Ref.
1	A coiled tubing kept in position by a round plastic frame	**Sensor:** water-responsive chromogenic reagent **Read-out:** external camera for time-stamped picture **Pros/Cons:** simple implementation/not thin film so rather bulky, the read-out relies on the post-processing of the picture taken from an external camera (semi-quantitative)	[36]
2	A bottom PDMS layer (thickness, 500 μm) embossed with appropriate relief geometry (uniform depth, 300 μm) and with a top-capping layer of PDMS that serves as a seal (thickness, 200 μm)	**Sensor:** water-responsive chromogenic reagent **Read-out:** picture taken from an external camera launched by near field communication chip for time **Pros/Cons:** simple design/ the read-out relies on the post-processing of the picture taken from an external camera (semi-quantitative)	[35]
3	Two main parts: (i) a microfluidic; and (ii) an electrical sensing component. The microfluidic channel is prepared with PDMS and is covalently bonded to PET containing sensing electrodes layer, via O_2 plasma etching and silanization. In some designs, the collection well is filled with a patterned SU8 filler coated with a thin saturated hydrogel layer that contacts skin for sweat uptake	**Sensor:** capacitive (analog/continuous). The sweat rate sensor contains two parallel Cr/Au spirals that are aligned with the microfluidic channel. Sweat rate is quantified by the change of impedance **Read-out:** external PCB for signal processing and communication via bluetooth **Pros/Cons:** quantitative read-out/the read-out signal depends also on the changing ionic concentration of the sweat	[34, 38]
4	Design similar to the one of device 3 but with the impedimetric sweat rate sensor formed by two electrodes with interdigitated fingers over which the serpentine channel repeatedly passes	**Sensor:** capacitive (digital/discrete). The multi electrodes design results in discrete/digital changes of the impedance that enable time-volume synchronization independently form the ionic concentration **Read-out:** external PCB for signal processing and communication via bluetooth **Pros/Cons:** quantitative read-out not depending on the ionic sweat concentration/ rather complex implementation (multiple electrodes)	[41]
5	The device is formed by three main layers: (i) an adhesive layer to strengthen the contact with the skin; (ii) a PDMS layer with microfluidics and electrodes for sensing; (iii) flexible PCB to connect electronics and communication chips	**Sensor:** the sensing mechanism relies on the measurement of the resistance between metal pads patterned onto the wall of the microfluidic channels. Two separate channels allow to solved the interdependence of the resistance on rate and electrical conductivity of the sweat. AC modulation is implemented to avoid the formation of electronic double layer that may foul the reading **Read-out:** flexible PCB for signal processing and communication via NFC **Pros/Cons:** quantitative read-out not depending on the ionic sweat concentration/rather complex implementation (two separate channels)	[40]
6	Design consists of (i) an adhesive layer; (ii) a PDMS microchannel; (iii) a PDMS PCB that connects two thermistors and a heater; and (iv) finally a PDMS cover. The design is simpler than the one of device 3 and 5 since it is rely on the direct measurement of the speed of the sweat flow rather than of the volume. The modular assembly facilitate the re-use of the PCB with with the disposable layers connected via magnets to the flexible PCB	**Sensor:** the device implements a flowmeter by reading the temperature difference between two thermistors. A heater positioned midway between the thermistors set their temperature which is identical before the flow of the sweat and that is different after. The difference of temperature yields a change of the resistance in the two thermistors **Read-out:** flexible PCB for signal processing and communication via BLE **Pros/Cons:** elegant solution implementing a micro-thin film flow-meter/sensitive to stretching because the distance between the two thermistors changes, the heater could be power hungry if not properly biased	[42]

AC: Alternate current; BLE: bluetooth low energy; PCB: printed circuit board; PDMS: polydimethylsiloxane; PET: polyethylene terephthalate.

analysis[50]. Currently, we register a few commercial devices that aim to track sweat rates and composition. One is KuduSmart (https://kudusmart.com/), and the other one is the GX patch (https://www.gatorade.com/equipment/gx-sweat-patch/gx-sweat-patch).

SWEATING - A SYMPTOM IN CLINICAL MEDICINE

Sweating is an unspecific but very common symptom in clinical medicine. Currently, the quantification of the sweat rate can only be conducted during clinical examination in this field. There are several qualitative measures (the Clinical Opioid Withdrawal Scale and the descriptive observation by the examinator) and quantitative measures (gravimetrical analysis using technical absorbents and determining changes in the body weight) that can be employed[51-53]. An easy, continuous, and straightforward measurement of the sweat rate during everyday life is not yet available. Therefore, the full clinical potential of sweating as a symptom and an indicator of health and diseases has only been vaguely exploited until recently.

Clinical sweat terminology

To objectively assess the symptom of "sweating", the sweat rate must be determined. It can be distinguished between local and whole body sweat rates. The local sweat rate refers to the excretion of sweat on a certain skin surface, whereas the whole body sweat rate covers the total loss of sweat from the body. Changes of the sweat rate can (i) result from either physiological and/or pathophysiological changes in the body, referred to as non-iatrogenic; or (ii) be induced in the body, for example, by pharmacological therapy, referred to as iatrogenic. The sweat rate may be increased above the physiological need in regard to maintaining thermoregulation, named hyperhidrosis, or decreased, named hypohydrosis[54]. When there is no sweat excretion at all, it is called anhidrosis. Derived from common medical terminology, changes in the sweat rate are classified as focal if a limited area on the body surface is affected or generalized if the whole-body surface is presumed to be affected. Changes in the sweat rate are categorized to be primary when originating within the functional chain of the sweat gland or secondary when induced by external variables affecting the sweat gland chain [Table 2][55].

Clinical sweat monitoring

Both the local and the whole body sweat loss assessments are not continuously feasible and need lab infrastructure. Wearable sweat analysis to assess hydration during exertion or in hot environments is convenient and affordable[37]. These wearable sweat sensors enable sweat rate monitoring and can additionally assess changes in electrolyte concentration such as sodium, chloride, and additional biomarkers of interest[46,56]. By being coupled to smartphones, wearable sweat sensors provide a straightforward opportunity to continuously assess the local sweat rate. This, in turn, makes it possible to extrapolate the whole body sweat loss[56]. Furthermore, learning algorithms enable direct data interpretation and use within predictive models to establish preventive measures or to adapt therapies.

Sweat in clinical medicine

Hyperhidrosis

Primary hyperhidrosis is an idiopathic condition that occurs in 4.8% of the U.S. population. The lead symptom is excessive sweating. The most affected regions are the plantar, palmar, and axillary regions of the body[57,58]. While not primarily being life-threatening, primary hyperhidrosis directly affects social life. More severe causes of hyperhidrosis can be assessed during clinical anamnesis and examination. One of the more prevalent symptoms of hyperhidrosis is night sweats, which is assessed by inquiring the patients if night sweats have been observed. The current clinical definition of night sweats is when pajamas had to be changed during the night as being soaked up wet. Due to the binary nature of the question, only the affirmative answer leads to documentation and, therefore, implementation into the treatment plan. In many instances, however, night sweats are not further investigated. Increased night sweats may have several underlying reasons, such as (i) elevated environmental conditions (temperature/relative humidity); (ii) infectious diseases such as viral infections with Influenza or COVID-19; and (iii) bacterial infections such as pneumonia and even tuberculosis. Additionally, night sweats may appear in cases of (iv) autoimmune diseases or (v) cancer. Also, (vi) hormone changes, such as those seen in hyperthyroidism; (vii) genetical

Table 2. Summary of the terminology of clinical sweat assessment

Umbrella term	Specification	Description
Sweat rate	Local	Sweat collected from a specific body surface over a specified time (indicated in $g{\cdot}h^{-1}{\cdot}m^{-2}$)
	Whole body sweat loss	Total amount of water lost due to sweating over a specified time
Causes of sweat rate changes	Iatrogenic	Sweat rate impacted through medical treatment or intervention
	Non-iatrogenic	Changes of the sweat rate that are not directly caused by medical treatment
Amount of sweat	Hyperhidrosis	Increased above the physiological need regarding the maintenance of the thermoregulation of the body
	Hypohidrosis	Decreased under the physiological need regarding the maintenance of the thermoregulation of the body
	Anhidrosis	No sweating
Changes in the amount of sweat rate	Focal	Specific locus on the body surface is affected
	Generalized	The whole-body surface is presumed to be affected
	Primary	Caused within the functional chain of the sweat gland
	Secondary	Due to external variables of the chain of the sweat gland

changes affecting the sweat gland function (e.g., in cystic fibrosis); (viii) brain infarction; or (ix) pharmacological treatments with amiodarone or hormone substitution, may lead to hyperhidrosis.

Hypohydrosis

Hypohydrosis can be categorized into exogenous, dermatological, and neurological causes[59]. Systemic neurohormonal inhibition of sweating or damage to skin and sweat glands can result from exogenous reasons. Congenital disorders lead to dermatological disorders, and neurological pathologies can be caused by autonomous dysfunction.

While hyperhidrosis can be an indicator of serious health deterioration, hypohydrosis is less often clinically significant. However, hypohydrosis can be an indicator of peripheral polyneuropathy such as in Diabetes Mellitus. Hypohydrosis can be assessed using one of the few established clinical sweat tests, namely the thermoregulatory sweat test (TST)[60]. For the TST, an indicator powder that changes color upon contact with sweat is applied to the skin. The person undergoing examination is subsequently exposed to environmental heat that usually leads to increased sweating. This process helps identify hypohydrotic skin areas.

CONCLUSION

Sweating is a common symptom in clinical medicine beyond sports science. Up to date, the absolute quantification of the sweat rate is challenging as the gold standard analysis by gravimetrical analysis is neither continuous nor feasible outside of a lab setting. These barriers are the main factors why sweat analysis has not been implemented in clinical medicine yet. Novel wearable sweat analyzing biosensors enable us to easily and continuously monitor the sweat rate independently of specialized laboratories. With the emergence of these novel biosensing devices, the sweat rate is accessible for structured clinical investigation and can serve as a novel digital biomarker. Importantly, cyber security, bioethical, and policy considerations need to be addressed for successful clinical implementation[61,62]. Clinical investigations are needed to demonstrate the additional clinical value of wearable sweat rate analysis for all stakeholders in healthcare.

DECLARATIONS

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Authors' contributions

Made substantial contributions to the conception and design of the Commentary: Brasier N, Niederberger C, Salvatore GA

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