Exploring Activity-Induced Lactate Pharmacokinetics: Implications for Minimally-Invasive Monitoring

A Literature Review

Vivien PERRELLE

August 30, 2023

1. Introduction

1.1. Sports applications of lactate monitoring

The monitoring of lactate levels holds significant importance in diagnosing and assessing various health conditions [1], including lactate acidosis and situations characterized by oxygen deficit, where lactate levels exceed accepted norms [2]. Although many medical applications, the demand for lactate monitoring solutions comes mainly from the sports domain. Lactate monitoring is instrumental in gauging training intensity and evaluating an athlete's endurance [3, 4]. Exercise-induced muscle fatigue is a reversible loss of muscle force (or muscle contractility) during work over time [5]. Human *in vivo* studies have demonstrated conspicuous concomitances between muscle lactate and proton concentrations, cellular pH, and muscle fatigue [6, 7]. Whether these concomitances reflect cause-effect relationships is still debated. Lactate has not been shown to cause muscle fatigue directly. Muscle lactate is, with interleukin-6 [8], a well-known and relevant biomarker of exercise-induced muscle fatigue [9–11]. Understanding and monitoring lactate levels allows athletes to adapt their training plans, optimize their workouts, prevent overtraining, and ultimately enhance their performance in their respective sports. Coaches and sports scientists interpret lactate data accurately and design training programs tailored to their needs and goals [3, 12].

Currently, lactate detection is mainly performed using blood sampling analyzers [13]. The most known hand-held blood lactate analyzers are the Lactate Pro, the Lactate Pro2, the Lactate Scout+, the Xpress, and the Edge [14]. Although reliable and accurate measurements are performed with such devices [14, 15], athletes must stop moving for blood collection from their fingertips or earlobes. Moreover, for lactate and any biomarkers, blood sampling is uncomfortable for users, cannot be used for continuous measurement, and is relatively expensive.

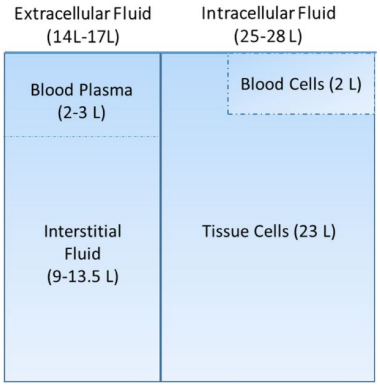

Figure 0.1: Distribution of water in the human body showing the approximate volume of blood plasma and ISF in the extracellular fluid compartment, and the volume of tissue and blood cells in the intracellular fluid compartment. From [16]

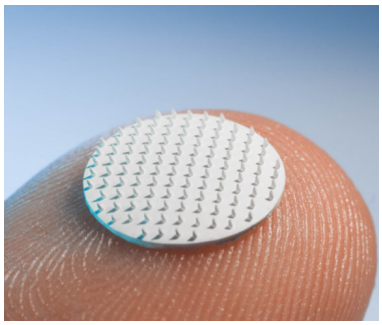

Figure 0.2: Illustration of a microneedles patch. From [17]

1.2. Microneedles technology for lactate monitoring

In recent years, developing non-invasive or minimally-invasive biosensors for continuous lactate monitoring has raised strong interest in wellness and sports applications. The two body fluids mainly considered by researchers to carry out these non-invasive measurements are sweat [18] and interstitial fluid (ISF) [19]. For detection in ISF, recent technology has proven its potential: microneedles [20]. Microneedles have been developed for various applications, including drug delivery, biosensing, and vaccination. They offer a minimally-invasive and user-friendly alternative to conventional needles, causing less pain and lower tissue damage [21]. Microneedles are fabricated using different techniques and materials, resulting in various types such as solid, dissolving, coated, and hollow microneedles [22]. In recent years, 3D printing has emerged as a promising technique for fabricating microneedle arrays, enabling point-of-care biosensing applications [21]. Additionally, microfluidic technology has been used to control the porosity of polylactic acid porous microneedles, allowing for adjustable ISF extraction efficiency [23]. Due to the small dimensions of microneedles (less than 1 mm in length), they penetrate the stratum corneum without reaching deep into the subcutaneous tissue, unlike the needle sensors used in commercially available CGM devices

[24]. The commercial maturity of minimally invasive biodetection in ISF is asserted yearly. **new biomarkers such as lactate could be monitored non-invasively with the emergence of microneedles biosensors** [25].

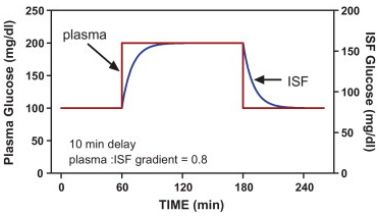

Figure 0.3: The lag time of glucose concentrations in the ISF is around 10 minutes compared with plasma concentrations. From [26]

1.2. Understanding lactate pharmacology for biosensor development

Understanding biomarkers' behavior in the organism is a prerequisite for biological detection research [27]. Clinical qualification is the evidentiary process of linking a biomarker with biological responses and clinical endpoints [28]. Clinicians evaluate the magnitude of the reason for the clinical cause of this biomarker production and establish a diagnosis. Studying biomarkers pharmacology is therefore essential before designing wearable biosensors.

A considerable body of clinical research has been devoted to glucose pharmacology in human ISF [29]. Although the state of the art is relatively well established for lactate as well [30], the lactic concentrations in the dermal ISF, in particular, remain relatively understudied. However, such clinical knowledge arouses growing interest, as biomonitoring technologies become increasingly mature and able to measure lactate concentrations in the skin painlessly.

The following work reviews the literature on lactate pharmacokinetics in the ISF during physical exercise. This state of knowledge aims to **highlight the relevance or irrelevance of dermal ISF as a medium for physical activity-induced lactate monitoring** and areas of persistent uncertainty.

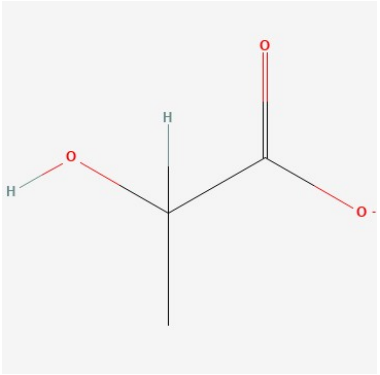

Figure 0.4: 2D Chemical Structure Depiction of Lactate.From [31]

2. Definitions

2.1. D-lactic acid & L-lactic acid

Lactic acid is a natural organic acid that can take the form of two enantiomers: *l-lactic acid* and *d-lactic acid*. **L-lactic acid is an endogenous compound involved in human energy metabolism** [32]. Tissue sources of l-lactate production include *erythrocytes*[1] , *hepatocytes*[2] , *skeletal myocytes*[3] , skin, and *astrocytes*[4] [34, 35]. On the other hand, d-lactic acid is produced in some less relevant metabolic pathways or by microorganisms strains [36]. Lactic acid bacteria produce lactic acid in the small intestine and colon [37, 38]. **Blood contains approximately 100 times more l-lactate than d-lactate** [3, 39]. Pathological significance of lactate is almost entirely confined to the l-lactate isoform [40]. It is the isoform routinely measured at the point of care [41] and in the laboratory [42].

1: Erythrocytes are red blood cells.

2: Hepatocytes are the chief functional cells of the liver[33].

3: Myocytes are muscle cells.

4: Astrocytes are a sub-type of cells in the central nervous system

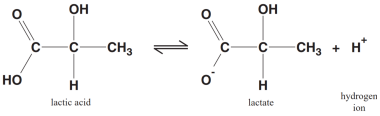

Figure 0.5: The dissociation of lactic acid. From [34]

2.2. Lactate & Lactic acid

Lactic acid is a natural organic acid that can take the form of two enantiomers: *l-lactic acid* and *d-lactic acid*. **L-lactic acid is an endogenous compound involved in human energy metabolism** [32]. Tissue sources of l-lactate production include *erythrocytes*[5] , *hepatocytes*[6] , *skeletal myocytes*[7] , skin, and *astrocytes*[8] [34, 35]. On the other hand, d-lactic acid

5: Erythrocytes are red blood cells.

6: Hepatocytes are the chief functional cells of the liver[33].

7: Myocytes are muscle cells.

8: Astrocytes are a sub-type of cells in the central nervous system

is produced in some less relevant metabolic pathways or by microorganism strains [36]. Lactic acid bacteria produce lactic acid in the small intestine and colon [37, 38]. **Blood contains approximately 100 times more l-lactate than d-lactate** [3, 39]. The pathological significance of lactate is almost entirely confined to the l-lactate isoform [40]. It is the isoform routinely measured at the point of care [41] and in the laboratory [42].

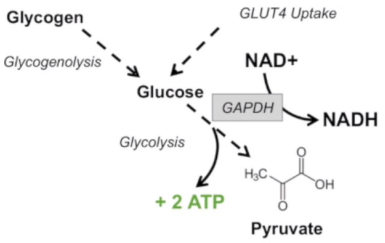

Figure 0.6: Pyruvate production in cells from glucose.

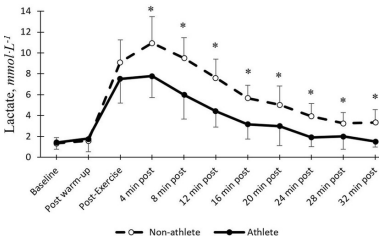

Figure 0.7: Blood lactate response in athletes vs. non-athletes. *Statistically significant difference between athletes vs. non-athletes (adjusted p<0.005). From [43]

3. Lactate metabolism & Cori cycle

3.1. Aerobic respiration & Anaerobic respiration

During rest and light physical activity, oxygen supply to cells is sufficient for *aerobic respiration*. Aerobic respiration is a cellular metabolism process by which cells break down carbohydrates and lipids to generate *adenosine triphosphate*[9] (ATP) molecules. Glucose molecules are formed from glycogen in the cell or supplied by the GLUT4 transporter from blood [45]. Glucose is broken down during the glycolysis process. *Nicotinamide adenine dinucleotide* (NAD+) co-enzyme catalyzes this reaction in the cytoplasm. The intermediate metabolite *pyruvate* is produced. If oxygen is abundant in the cell, pyruvate can enter the mitochondria, generating 32 to 38 ATP. Intense exercises cause cellular hypoxia and lead to anaerobic metabolism. *Anaerobic respiration* is the process by which skeletal muscle cells produce energy without oxygen. **The *Cori cycle*, also known as the Lactic acid cycle, describes the metabolic pathway of lactic acid produced during anaerobic metabolism by skeletal muscle cells** [46]. Instead of entering the mitochondrial matrix, excess pyruvate is catalyzed with Nicotinamide adenine dinucleotide (NADH) by lactate dehydrogenase (LDH) enzyme into lactic acid. LDH has a greater binding affinity for l-lactate than d-lactate [47]. D-lactate is, when present, metabolized at a slower rate.

9: ATP is the energy source for use and storage at the cellular level [44].

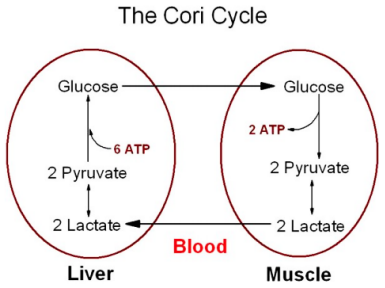

Figure 0.8: Corri cycle schematic overview. From [48].

3.2. Muscle lactate release

High lactic acid production can cause lactic acid acidosis[10] in muscle cells [53, 54]. The monocarboxylate transporter MCT1[11] avoid acidosis by evacuating lactic acid from the muscle cell to the blood [56, 57]. Lactate is buffered in plasma by bicarbonate of soda ($NaHCO_3$) [34]. **Lactic acid accumulates in contracting muscle and blood, beginning around 50-70% of the maximal O_2 uptake**, well before the aerobic capacity is fully utilized [58]. The predominant explanation is that lactate production during submaximal dynamic exercise is not O_2 dependent [59].

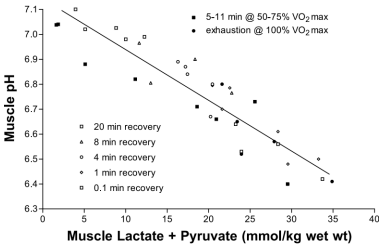

Figure 0.9: Figure redrawn from data from Sahlin et al. [49] (Figs. 1 and 2, p. 46), showing the linear relationship between the sum of muscle lactate and pyruvate vs. muscle pH. Data are combined from different exercise intensities and different durations of recovery after exercise to exhaustion. From [50].

3.3. Lactate fate in the organism

Lactate produced during exercise muscle is distributed unevenly throughout the body's different compartments [51]. The anaerobic component of cellular metabolism can be theoretically assessed by measuring lactic flux at the cellular level or the level of the isolated muscle [60]. At the whole organism level, blood measurements are more complex to be relevantly interpreted as a muscle fatigue indicator due to the actions of different bodies on the lactic flux, the action of unused

muscles, and the multicompartmental diffusion of lactate [60]. Different compartmental models have been formulated to predict blood lactate concentration ($[La^-]_{blo}$) [61–67]. Although some show promising results, these models have limitations. They usually include many assumptions not applicable to continuous monitoring, such as when the maximum post-exercise $[La^-]_{blo}$ will be reached, a glycogen fixed concentration, or specific stimulation intensities or durations. Although they do not make it possible to formulate complete models, the advances made in recent years provide answers regarding the distribution of lactate in the different compartments of the body.

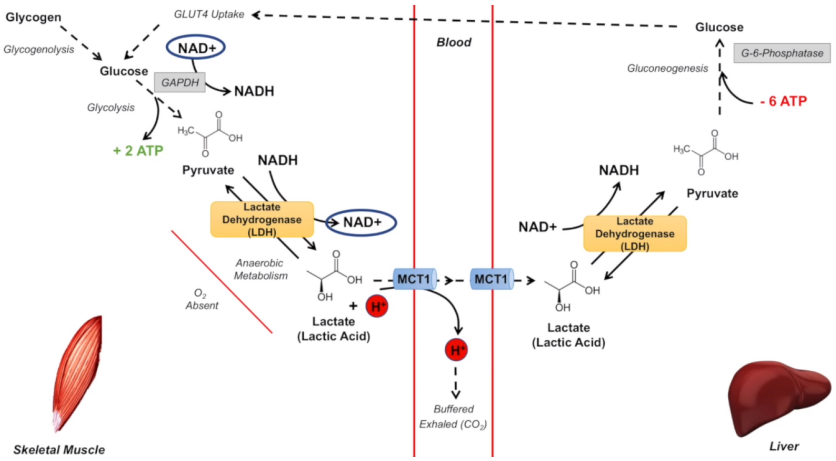

Figure 0.11: Simplified illustration of the Cori cycle. From [68]

4. Lactate pharmacokinetics during exercise

Lactate produced during exercise muscle is distributed unevenly throughout the body's different compartments [51]. The anaerobic component of cellular metabolism can be theoretically assessed by measuring lactic flux at the cellular level or the level of the isolated muscle [60]. At the whole organism level, blood measurements are more complex to be relevantly interpreted as a muscle fatigue indicator due to the actions of different bodies on the lactic flux, the action of unused muscles, and the multicompartmental diffusion of lactate [60]. Different compartmental models have been formulated to predict blood lactate concentration ($[La^-]_{blo}$) [61–67]. Although some show promising results, these models have limitations. They usually include many assumptions not applicable to continuous monitoring, such as when the maximum post-exercise $[La^-]_{blo}$ will be reached, a glycogen fixed concentration, or specific stimulation intensities or durations. Although they do not make it possible to formulate complete models, the advances made in recent years provide answers regarding the distribution of lactate in the different compartments of the body.

4.1. Muscle versus blood lactate concentrations

$[La^-]_{blo}$ results from global lactate appearance and disappearance, not only the lactate appearance and disappearance of the stimulated muscle fibers [6, 69]. The lactate transport from the active muscle to the

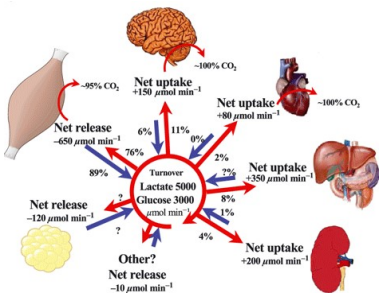

Figure 0.10: Scheme of tissue contributions to systemic lactate turnover in healthy humans during moderate intensity exercise. From [51]

10: Lactic acidosis is defined as a blood lactate concentration of 5 mmol/L and a pH lower than 7.35 [52].

11: Monocarboxylate transporters (MCTs) catalyze the proton-linked transport of monocarboxylates such as L-lactate, pyruvate, and the ketone bodies across the plasma membrane [55].

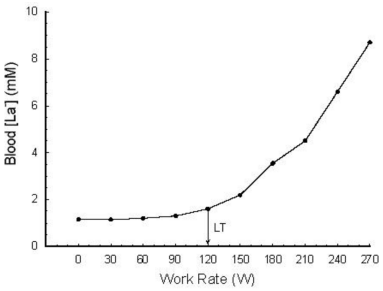

Figure 0.12: A typical [La-]b response to a progressive, incremental exercise test. LT represents the "lactate threshold." These are whole blood measurements corrected for water content. From [3]

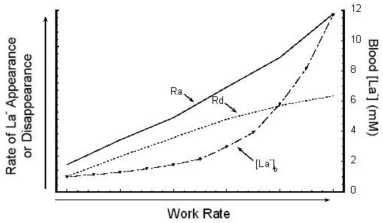

Figure 0.13: Schematic view of Lactate rate of appearance (Ra), Lactate rate of disappearance (Rd), and resulting $[La^-]_{blo}$ during progressive, incremental exercise. From [69]

blood, which depends on the concentration gradient, also plays a role [6]. Despite the complexity of the phenomena to be taken into consideration, numerous pieces of evidence demonstrate that **active muscle lactate concentration ($[La^-]_{mus}$) presents similar patterns to those of $[La^-]_{blo}$** [70–73].

4.2. Whole blood versus plasma lactate concentrations

Several studies show an inhomogeneous distribution of lactate in blood during graded exercise [74–77]. According to their membrane potential, the erythrocytes' intracellular concentration is lower than the plasma lactate concentration ($[La^-]_{pla}$) [3, 76, 78]. **Consequently, whole $[La^-]_{blo}$ must be differentiated from $[La^-]_{pla}$**. The whole blood-plasma lactate concentration ratio might vary from 63% to 81% depending on plasma water content and hematocrit[12] [3]. **$[La^-]_{pla}$ is, around 1.5 times higher than whole $[La^-]_{blo}$ at rest**[13] [81–83]. This ratio increases during rapid and graded exercise-induced lactate releases [74, 78]. This distinction is a significant issue for blood lactate measurements. Indeed, different lactate analyzers measure plasma or whole blood lactate concentration. **Which concentration is measured by point-of-care devices could be unclear** [3]. $[La^-]_{pla}$ is traditionally measured in central laboratories.

4.3. Arterial versus capillary blood lactate concentrations

Arterial blood is the standard sample for laboratory lactate measurement [84]. It gives a reliable indication of global appearance and disappearance [85]. **At rest, arterial lactate and capillary lactate are weakly correlated** [83]. Several studies demonstrate that capillary plasma lactate concentration ($[La^-]_{cap}$) and hand-held point-of-care (POC) device measurements are significantly higher than arterial plasma lactate concentration ($[La^-]_{art}$) and its measurements in laboratory [86–88]. The magnitude of this bias varies between studies [85]. Unlike well-validated central laboratory equipment, hand-held POC devices do not provide sufficiently relevant clinical data to draw medical diagnoses[89, 90]. **However, correlation between $[La^-]_{art}$ and $[La^-]_{cap}$ increases during physical exercise** [83]. Although capillary blood samples for in-hospital medical diagnostics remain debated, **capillary lactate measurements are consistently usable for sports training applications** [83, 91, 92].

4.4. Absolute capillary blood lactate concentrations versus portable analyzers measurements during exercise

The most important study on commercialized portable blood lactate analyzers since 2015 was led by J. M. Bonaventura et al. [93]. They realized a comparative study on five hand-held blood lactate analyzers. They tested the devices on venous blood samples. **The devices' reliability was generally lower than 0.5 mM for concentrations of 1.0 to 10 mM**. For all five portable analyzers, the analytical error within a brand was much smaller than the biological variation in venous blood lactate. **Compared with a criterion blood lactate analyzer, all portable analyzers tend to under-read (i.e., a negative bias), particularly evident at the highest concentrations (15 to 23 mM)** [93, 94].

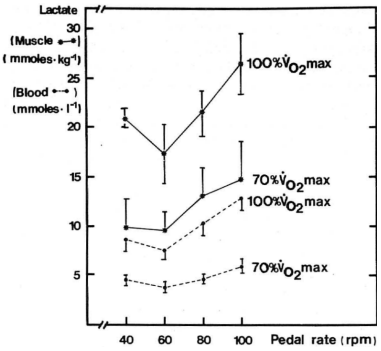

Figure 0.14: $[La^-]_{mus}$ (stars) and $[La^-]_{blo}$ (dots) for submaximal (70%Vo2max) and maximal (100%Vo2max) exercise intensity in six healthy male subjects during bicycling exercises. From [70]

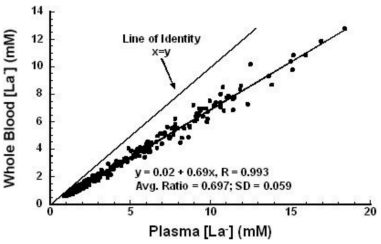

Figure 0.15: Whole $[La^-]_{blo}$ versus corresponding $[La^-]_{pla}$. SD: standard deviation of $[La^-]_{blo}$ to $[La^-]_{pla}$ ratio. N = 324 blood samples. From [3]

12: The hematocrit is the volume percentage of red blood cells in blood

13: In comparison, plasma glucose values are about 10% - 15% higher than whole blood when the hematocrit is normal [79, 80].

Figure 0.16: Picture of the Lactate Pro 2, a commercially available blood lactate analyzer.

4.5. Capillary blood versus interstitial lactate concentrations

The inherent biological attributes of ISF complement its practical advantages. Analytes in interstitial fluid (ISF) come from the blood through continuous capillaries[14] . Pores of their lining only allow small solutes, under approximately 70kDa, to pass across the capillary wall[95, 96]. Lactate molecular weight being 90 Da, it highly diffuses into the ISF and **Lactate ISF concentration ($[La^-]_{ISF}$) has a nearly 1:1 ratio correlation with $[La^-]_{cap}$** [30]. ISF biomarker concentrations are similar to plasma concentrations for low molecular weight species, and the blood-to-ISF lag time is between 5 to 15 minutes [30].

4.6. Dermal interstitial lactate concentrations

In healthy people, skin lactate concentration at rest is between 1 and 2.5 mmol/l [99]. **Resting dermal $[La^-]_{ISF}$ is in average about 30% higher than arterial $[La^-]_{pla}$** [99, 100]. Indeed, $[La^-]_{pla}$ at rest comprises between 0.5mmol/l and 2mmol/l in healthy humans, depending on people and time [101]. Like other tissues, the skin releases lactate. Skin contributes about 5% at rest to the whole-body lactate turnover [97]. However, despite the high proportion of whole-body lactate production by skin, **the evolution over time at rest of skin lactate concentration appear to reflect the evolution of the plasma concentration relatively well** [97]. The efficient blood-ISF bilateral diffusion of lactate seems to explain this correlation. As for glucose, lactate is subject to the inherent plasma-to-ISF lag [30]. An insufficient number of physiological studies address this delay for lactate. However, recent non-commercialized microneedle-based lactate biosensors suggest **a measured lag time of approximately 10 minutes relative to plasma variations** [102, 103]. The subcutaneous depth of the capillary plexus varies between 0.6 and 1.5 mm, depending on the on-body location [104]. Consequently, the delay between $[La^-]_{ISF}$ at the microneedles location and $[La^-]_{pla}$ may vary depending on the on-body location and Microneedles subcutaneous depth.

To our knowledge, **no study deals with the correlation between dermal $[La^-]_{ISF}$ and arterial $[La^-]_{pla}$ during exercise**. However, the net production of lactate by the muscles increases drastically during exercise compared to other organs, including the skin [51]. Consequently, the correlation between $[La^-]_{ISF}$ and $[La^-]_{pla}$ is probably better during exercise than at rest. Further studies remain necessary to quantify this correlation and possible parameters to be considered, such as the location on the body of the dermal ISF sampling and its proximity to the producing muscles. In addition, the dermal lactic concentration could vary depending on the depth under the skin. Krogstad et al. suggest a possible negative linear relationship between the catheter location in the dermal tissue layer and dermal $[La^-]_{ISF}$ during microdialysis measurements [105]. **Further studies are needed to confirm and quantify the influence of the microneedles depth of a minimally-invasive lactate monitoring device**.

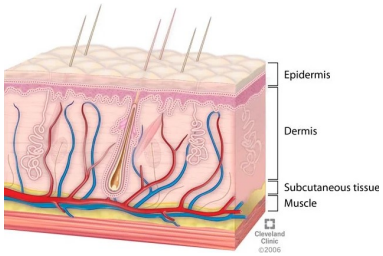

Figure 0.17: Schematic representation of the skin layers.

14: Depending on the location, continuous capillaries are generally the most present in the skin, and the least porous capillary type.

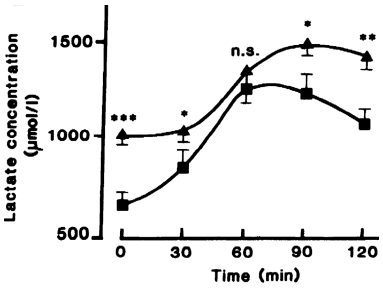

Figure 0.18: Evolution of $[La^-]_{pla}$ (square) and dermal $[La^-]_{ISF}$ (triangle) during an oral glucose tolerance test. From [97]

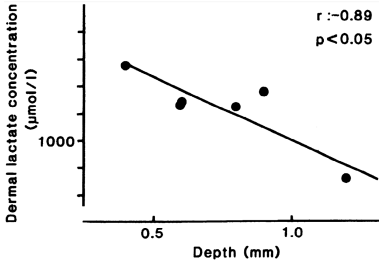

Figure 0.19: Measurement (n=6) of dermal concentration in either abdominal or forearm skin depends on the dermal tissue's catheter depth according to a linear relationship (R=-0.89, P < 0.05). From [97]

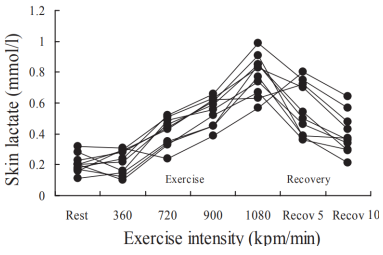

Figure 0.20: Lactate concentration of skin surface on working muscle at rest, during cycle exercise and recovery when one subjects performed the same exercise ten times. From [98]

5. Conclusion

We provide a comprehensive literature review on lactate pharmacology in the human body and lactic concentrations in ISF during physical exercise. This state-of-the-art analysis contributes to understanding lactic acid evolution and ISF monitoring during physical effort. This investigation of lactate diffusivity status aims to provide synthesized and actionable information to biosensor developers. The main takeaways are synthesized below.

During exercise, lactate is mainly released from muscle tissue. Synthesized by skeletal muscle cells, lactate diffuses throughout the body from the ISF of muscle cells to plasma, then from capillary vessels to the subcutaneous and dermal ISF. Lactate's low molecular weight and high diffusivity suggest similar and correlated concentrations in extracellular fluid [30]. Few data are available on lactic acid concentrations in the skin and their variations during physical effort. Despite a consortium on the correlation between blood and interstitial concentrations, uncertainties in measurements of dermal ISF concentration remain greater than for glucose [106]. Depth in the dermis seems to have an impact on measured levels. Hydration may also be a factor in blood-tissue lactate crosstalk [106]. These parameters must be investigated to characterize the medical relevance of its monitoring in dermal ISF. **Further studies on lactate pharmacology are required to develop relevant, accurate, minimally-invasive lactate biosensors.**

References

[1] Xiaolu Li et al. 'Lactate metabolism in human health and disease'. In: Signal transduction and targeted therapy 7.1 (2022), p. 305 (cited on page 1).

[2] Christopher D Foucher and Robert E Tubben. 'Lactic acidosis'. In: StatPearls [Internet. StatPearls Publishing, 2022 (cited on page 1).

[3] Matthew L Goodwin et al. 'Blood lactate measurements and analysis during exercise: a guide for clinicians'. In: Journal of diabetes science and technology 1.4 (2007), pp. 558–569 (cited on pages 1–5).

[4] I. Jacobs. 'Blood lactate. Implications for training and sports performance'. In: Sports Medicine (Auckland, N.Z.) 3.1 (1986), pp. 10–25. DOI: 10.2165/00007256-198603010-00003 (cited on page 1).

[5] HR Gosker and AMWJ Schols. Fatigued muscles in COPD but no finishing line in sight. 2008 (cited on page 1).

[6] Simeon P Cairns. 'Lactic acid and exercise performance'. In: Sports medicine 36.4 (2006), pp. 279–291 (cited on pages 1, 4, 5).

[7] L Messonnier and H Dubouchaud. 'Le lactate: sa cinétique, son métabolisme, ses relations avec la performance et ses controverses'. In: Science & Motricité 70 (2010), pp. 21–30 (cited on page 1).

[8] Bente Klarlund Pedersen, Adam Steensberg, and Peter Schjerling. 'Exercise and interleukin-6'. In: Current opinion in hematology 8.3 (2001), pp. 137–141 (cited on page 1).

[9] Josef Finsterer. 'Biomarkers of peripheral muscle fatigue during exercise'. In: BMC musculoskeletal disorders 13.1 (2012), pp. 1–13 (cited on page 1).

[10] Jing-jing Wan et al. 'Muscle fatigue: general understanding and treatment'. In: Experimental & molecular medicine 49.10 (2017), e384–e384 (cited on page 1).

[11] George Theofilidis et al. 'Monitoring exercise-induced muscle fatigue and adaptations: making sense of popular or emerging indices and biomarkers'. In: Sports 6.4 (2018), p. 153 (cited on page 1).

[12] L Véronique Billat. 'Use of blood lactate measurements for prediction of exercise performance and for control of training'. In: Sports medicine 22.3 (1996), pp. 157–175 (cited on page 1).

[13] D. B. Pyne et al. 'Evaluation of the Lactate Pro blood lactate analyser'. In: European Journal of Applied Physiology 82.1 (May 2000), pp. 112–116. DOI: 10.1007/s004210050659 (cited on page 1).

[14] Jacinta M. Bonaventura et al. 'Reliability and Accuracy of Six Hand-Held Blood Lactate Analysers'. In: Journal of Sports Science & Medicine 14.1 (Jan. 27, 2015), pp. 203–214. (Visited on 09/07/2023) (cited on page 1).

[15] Halil İbrahim Kaya et al. 'İki Farkli Taşinabilir Elektro-Enzimatik Laktat Analiz Cihazinin Geçerlilik ve Güvenilirlik Çalişmasi'. In: Spor Hekimligi Dergisi 55.2 (2020). Publisher: Türkiye Spor Hekimleri Dernegi, pp. 138–147. DOI: 10.5152/tjsm.2020.170. (Visited on 09/07/2023) (cited on page 1).

[16] Julia Madden et al. 'Biosensing in dermal interstitial fluid using microneedle based electrochemical devices'. In: Sensing and Bio-Sensing Research 29 (2020), p. 100348 (cited on page 1).

[17] MyLife Technologies. Revolutionizing Vaccine Delivery with Ceramic Microneedles (cited on page 1).

[18] Xing Xuan et al. 'Lactate biosensing for reliable on-body sweat analysis'. In: ACS sensors 6.7 (2021), pp. 2763–2771 (cited on page 1).

[19] Wei Gao, George A Brooks, and David C Klonoff. 'Wearable physiological systems and technologies for metabolic monitoring'. In: Journal of applied physiology 124.3 (2018), pp. 548–556 (cited on page 1).

[20] P Dardano, I Rea, and L De Stefano. 'Microneedles-based electrochemical sensors: New tools for advanced biosensing'. In: Current Opinion in Electrochemistry 17 (2019), pp. 121–127 (cited on page 1).

[21] Misagh Rezapour Sarabi, Sattar Akbari Nakhjavani, and Savas Tasoglu. '3D-Printed Microneedles for Point-of-Care Biosensing Applications'. In: Micromachines 13.7 (July 13, 2022), p. 1099. DOI: 10.3390/mi13071099. (Visited on 09/07/2023) (cited on page 1).

[22] Apoorva Panda et al. 'Fabrication and development of controlled release PLGA microneedles for macromolecular delivery using FITC-Dextran as model molecule'. In: Journal of Drug Delivery Science and Technology 68 (Feb. 2022), p. 102712. DOI: 10.1016/j.jddst.2021.102712 (cited on page 1).

[23] Boyu Qin et al. 'Porosity control of polylactic acid porous microneedles using microfluidic technology'. In: 2022 IEEE CPMT Symposium Japan (ICSJ) (Nov. 9, 2022), pp. 127–130. DOI: 10.1109/ICSJ55786.2022.10034733 (cited on page 1).
[24] Letizia Ventrelli, Lucanos Marsilio Strambini, and Giuseppe Barillaro. 'Microneedles for transdermal biosensing: current picture and future direction'. In: Advanced healthcare materials 4.17 (2015), pp. 2606–2640 (cited on page 2).
[25] Mark Friedel et al. 'Opportunities and challenges in the diagnostic utility of dermal interstitial fluid'. In: Nature Biomedical Engineering (2023), pp. 1–15 (cited on page 2).
[26] D Barry Keenan et al. 'Interstitial fluid glucose time-lag correction for real-time continuous glucose monitoring'. In: Biomedical signal processing and control 8.1 (2013), pp. 81–89 (cited on page 2).
[27] Robert M Califf. 'Biomarker definitions and their applications'. In: Experimental Biology and Medicine 243.3 (2018), pp. 213–221 (cited on page 2).
[28] John A Wagner. 'Overview of biomarkers and surrogate endpoints in drug development'. In: Disease markers 18.2 (2002), pp. 41–46 (cited on page 2).
[29] Boyu Zhu et al. 'An overview of wearable and implantable electrochemical glucose sensors'. In: Electroanalysis 34.2 (2022), pp. 237–245 (cited on page 2).
[30] Jason Heikenfeld et al. 'Accessing analytes in biofluids for peripheral biochemical monitoring'. In: Nature biotechnology 37.4 (2019), pp. 407–419 (cited on pages 2, 6, 7).
[31] National Center for Biotechnology Information. 'PubChem Compound Summary for CID 91435, Lactate'. In: (). Consulted on August 18, 2022 (cited on page 2).
[32] Joshua D Rabinowitz and Sven Enerbäck. 'Lactate: the ugly duckling of energy metabolism'. In: Nature Metabolism 2.7 (2020), pp. 566–571 (cited on page 2).
[33] Zhou Zhou, Ming-Jiang Xu, and Bin Gao. 'Hepatocytes: a key cell type for innate immunity'. In: Cellular & molecular immunology 13.3 (2016), pp. 301–315 (cited on page 2).
[34] Barrie Phypers and JM Tom Pierce. 'Lactate physiology in health and disease'. In: Continuing Education in Anaesthesia, 6.3 (2006), pp. 128–132 (cited on pages 2, 3).
[35] Pierre J Magistretti and Igor Allaman. 'Lactate in the brain: from metabolic end-product to signalling molecule'. In: Nature Reviews Neuroscience 19.4 (2018), pp. 235–249 (cited on page 2).
[36] Miroslav Pohanka. 'D-lactic acid as a metabolite: toxicology, diagnosis, and detection'. In: BioMed Research International 2020 (2020) (cited on pages 2, 3).
[37] Shui Ping Wang et al. 'Pivotal roles for pH, lactate, and lactate-utilizing bacteria in the stability of a human colonic microbial ecosystem'. In: Msystems 5.5 (2020), e00645–20 (cited on pages 2, 3).
[38] Alain L Servin. 'Antagonistic activities of lactobacilli and bifidobacteria against microbial pathogens'. In: FEMS microbiology reviews 28.4 (2004), pp. 405–440 (cited on pages 2, 3).
[39] Satish K Tuteja, Connor Ormsby, and Suresh Neethirajan. 'Noninvasive label-free detection of cortisol and lactate using graphene embedded screen-printed electrode'. In: Nano-micro letters 10.3 (2018), pp. 1–10 (cited on pages 2, 3).
[40] Kamel S Kamel, Man S Oh, and Mitchell L Halperin. 'L-lactic acidosis: pathophysiology, classification, and causes; emphasis on biochemical and metabolic basis'. In: Kidney International 97.1 (2020), pp. 75–88 (cited on pages 2, 3).
[41] Francesca Miranda Di Mauro and Gretchen Lee Schoeffler. 'Point of care measurement of lactate'. In: Topics in companion animal medicine 31.1 (2016), pp. 35–43 (cited on pages 2, 3).
[42] Michael Dacko and Thomas Lange. 'Improved detection of lactate and β-hydroxybutyrate using MEGA-sLASER at 3 T'. In: NMR in Biomedicine 32.7 (2019), e4100 (cited on pages 2, 3).
[43] Jessica N Hinojosa, Christopher M Hearon, and Robert J Kowalsky. 'Blood lactate response to active recovery in athletes vs. non-athletes'. In: Sport Sciences for Health 17.3 (2021), pp. 699–705 (cited on page 3).
[44] Jacob Dunn and Michael H Grider. 'Physiology, adenosine triphosphate'. In: StatPearls [Internet. StatPearls Publishing, 2021 (cited on page 3).
[45] Shaohui Huang and Michael P Czech. 'The GLUT4 glucose transporter'. In: Cell metabolism 5.4 (2007), pp. 237–252 (cited on page 3).
[46] American Chemical Society National Historic Chemical Landmarks. Carl and Gerty Cori and Carbohydrate Metabolism Accessed on July 24th, 2022 (cited on page 3).

[47] Jan P. Kovacic. 'Chapter 60 - Lactic Acidosis'. In: (2009), pp. 254–257. DOI: 10.1016/B978-1-4160-2591-7.10060-8 (cited on page 3).
[48] How anaerobic metabolism still contributes to VO2? Accessed on July 26th, 2022 (cited on page 3).
[49] K Sahlin et al. 'Effects of lactic acid accumulation and ATP decrease on muscle tension and relaxation'. In: American Journal of Physiology-Cell Physiology 240.3 (1981), pp. C121–C126 (cited on page 3).
[50] Robert A Robergs, Farzenah Ghiasvand, and Daryl Parker. 'Biochemistry of exercise-induced metabolic acidosis'. In: American Journal of Physiology-Regulatory, Integrative and Comparative Physiology (2004) (cited on page 3).
[51] Gerrit Van Hall. 'Lactate kinetics in human tissues at rest and during exercise'. In: Acta physiologica 199.4 (2010), pp. 499–508 (cited on pages 3, 4, 6).
[52] Sean M Forsythe and Gregory A Schmidt. 'Sodium bicarbonate for the treatment of lactic acidosis'. In: Chest 117.1 (2000), pp. 260–267 (cited on page 4).
[53] Jeffrey A Kraut and Nicolaos E Madias. 'Lactic acidosis'. In: New England Journal of Medicine 371.24 (2014), pp. 2309–2319 (cited on page 3).
[54] Nicolaos E Madias. 'Lactic acidosis'. In: Kidney international 29.3 (1986), pp. 752–774 (cited on page 3).
[55] Andrew P Halestrap and Marieangela C Wilson. 'The monocarboxylate transporter family—role and regulation'. In: IUBMB life 64.2 (2012), pp. 109–119 (cited on page 4).
[56] KJ McCullagh et al. 'Role of the lactate transporter (MCT1) in skeletal muscles'. In: American Journal of Physiology-Endo 271.1 (1996), E143–E150 (cited on page 3).
[57] RL Hazelwood. 'Carbohydrate metabolism'. In: Avian physiology. Springer, 1986, pp. 303–325 (cited on page 3).
[58] GA Brooks. 'Lactate production under fully aerobic conditions: the lactate shuttle during rest and exercise.' In: Federation proceedings. Vol. 45. 13. 1986, pp. 2924–2929 (cited on page 3).
[59] A t Katz and K Sahlin. 'Regulation of lactic acid production during exercise'. In: Journal of applied physiology 65.2 (1988), pp. 509–518 (cited on page 3).
[60] F Carré. 'Répartition du lactate dans l'organisme après un exercice musculaire: le modèle historique unicompartimental et ses limites'. In: Science & sports 8.3 (1993), pp. 189–191 (cited on pages 3, 4).
[61] H Freund and P Zouloumian. 'Lactate after exercise in man: I. Evolution kinetics in arterial blood'. In: European Journal of Applied Physiology and Occupational Physiology 46.2 (1981), pp. 121–133 (cited on page 4).
[62] P Zouloumian and H Freund. 'Lactate after exercise in Man: II. Mathematical model.' In: European journal of applied phy 46.2 (1981), pp. 135–147 (cited on page 4).
[63] P Zouloumian and H Freund. 'Lactate after exercise in man: III. Properties of the compartment model'. In: European Journal of Applied Physiology and Occupational Physiology 46.2 (1981), pp. 149–160 (cited on page 4).
[64] H Freund and P Zouloumian. 'Lactate after exercise in man: IV. Physiological observations and model predictions'. In: European Journal of Applied Physiology and Occupational Physiology 46.2 (1981), pp. 161–176 (cited on page 4).
[65] A Zerman, C Cobelli, and L Sacca. 'A Compartmental Model Of Lactate Kinetics In Humans: Role Of Sites Of Tracer Administration And Sampling'. In: [1990] Proceedings of the Twelfth Annual International Conference o IEEE. 1990, pp. 959–960 (cited on page 4).
[66] Ralph Beneke, Masen D Jumah, and Renate M Leithäuser. 'Modelling the lactate response to short-term all out exercise'. In: Dynamic medicine 6.1 (2007), pp. 1–7 (cited on page 4).
[67] John F Moxnes and Øyvind Sandbakk. 'The kinetics of lactate production and removal during whole-body exercise'. In: Theoretical Biology and Medical Modelling 9.1 (2012), pp. 1–14 (cited on page 4).
[68] JJ Medicine YouTube channel. Cori Cycle - Lactic Acid Metabolism - Purpose and Importance in Anaerobic Metabolism Accessed on July 26th, 2022 (cited on page 4).
[69] George A Brooks. 'Anaerobic threshold: review of the concept and directions for future research.' In: Medicine and science in sports and exercise 17.1 (1985), pp. 22–34 (cited on page 4).
[70] HERBERT Löllgen, TERRY Graham, and GISELA Sjogaard. 'Muscle metabolites, force, and perceived exertion bicycling at varying pedal rates'. In: Med Sci Sports Exerc 12.5 (1980), pp. 345–51 (cited on page 5).

[71] L Bruce Gladden. 'Lactate metabolism during exercise'. In: MEDICINE AND SPORT SCIENCE 46 (2004), pp. 152–196 (cited on page 5).
[72] J Karlsson, B Diamant, and B Saltin. 'Muscle metabolites during submaximal and maximal exercise in man'. In: Scandinavian journal of clinical and laboratory investigation 26.4 (1970), pp. 385–394 (cited on page 5).
[73] Ira Jacobs and Peter Kaiser. 'Lactate in blood, mixed skeletal muscle, and FT or ST fibres during cycle exercise in man'. In: Acta physiologica scandinavica 114.3 (1982), pp. 461–466 (cited on page 5).
[74] Michael J Buono and John E Yeager. 'Intraerythrocyte and plasma lactate concentrations during exercise in humans'. In: European journal of applied physiology and occupational physiology 55.3 (1986), pp. 326–329 (cited on page 5).
[75] ROBERT T Harris and GARY A Dudley. 'Exercise alters the distribution of ammonia and lactate in blood'. In: Journal of Applied Physiology 66.1 (1989), pp. 313–317 (cited on page 5).
[76] Peter Foxdal et al. 'Lactate concentration differences in plasma, whole blood, capillary finger blood and erythrocytes during submaximal graded exercise in humans'. In: European Journal of Applied Physiology and Occupat 61.3 (1990), pp. 218–222 (cited on page 5).
[77] EDITH W Smith et al. 'Lactate distribution in the blood during progressive exercise.' In: Medicine and science in sports a 29.5 (1997), pp. 654–660 (cited on page 5).
[78] Carsten Juel et al. 'Lactate and potassium fluxes from human skeletal muscle during and after intense, dynamic, knee extensor exercise'. In: Acta physiologica Scandinavica 140.2 (1990), pp. 147–159 (cited on page 5).
[79] Narendra Kotwal and Aditi Pandit. 'Variability of capillary blood glucose monitoring measured on home glucose monitoring devices'. In: Indian journal of endocrinology and metabolism 16.Suppl 2 (2012), S248 (cited on page 5).
[80] Hye Soon Kim. 'Blood glucose measurement: is serum equal to plasma?' In: Diabetes & Metabolism Journal 40.5 (2016), pp. 365–366 (cited on page 5).
[81] A REETA PÖSÖ, KIMMO J LAMPINEN, and LEENA A RÄSÄNEN. 'Distribution of lactate between red blood cells and plasma after exercise'. In: Equine Veterinary Journal 27.S18 (1995), pp. 231–234 (cited on page 5).
[82] NM Koho, LK Väihkönen, and AR Pösö. 'Lactate transport in red blood cells by monocarboxylate transporters'. In: Equine Veterinary Journal 34.S34 (2002), pp. 555–559 (cited on page 5).
[83] JR Williams, N Armstrong, and BJ Kirby. 'The influence of the site of sampling and assay medium upon the measurement and interpretation of blood lactate responses to exercise'. In: Journal of sports sciences 10.2 (1992), pp. 95–107 (cited on page 5).
[84] S Oyono-Enguelle et al. 'Comparison of arterial and venous blood lactate kinetics after short exercise'. In: International journal of sports medicine 10.01 (1989), pp. 16–24 (cited on page 5).
[85] Chris Higgins. Lactate measurement: arterial versus venous blood sampling. January 2017. Accessed on August 17, 2022 (cited on page 5).
[86] Olivier Collange et al. 'Comparison of capillary and arterial lactate levels in patients with shock'. In: Anaesthesia Critical Care & Pain Medicine 36.3 (2017), pp. 157–162 (cited on page 5).
[87] Leandro Seoane et al. 'Capillary lactic acid validation in an ED'. In: The American journal of emergency medicine 31.9 (2013), pp. 1365–1367 (cited on page 5).
[88] Anette Raa et al. 'Validation of a point-of-care capillary lactate measuring device (Lactate Pro 2)'. In: Scandinavian journal of trauma, resuscitation and emergency medicine 28.1 (2020), pp. 1–7 (cited on page 5).
[89] Colin A Graham et al. 'Agreement between capillary and venous lactate in emergency department patients: prospective observational study'. In: BMJ open 9.4 (2019), e026109 (cited on page 5).
[90] David Stoll et al. 'Capillary and venous lactate measurements with a handheld device compared to venous blood-gas analysis for emergency patients'. In: Scandinavian Journal of Trauma, Resuscitation and Emergency Me 26.1 (2018), pp. 1–5 (cited on page 5).
[91] Pattharawin Pattharanitima et al. 'Correlation of arterial, central venous and capillary lactate levels in septic shock patients'. In: Journal of the Medical Association of Thailand 94.2 (2011), p. 175 (cited on page 5).

[92] Bryan Lightowler and Anthony Hoswell. 'Can handheld POC capillary lactate measurement be used with arterial and venous laboratory testing methods in the identification of sepsis?' In: Journal of Paramedic Practice 8.8 (2016), pp. 396–406 (cited on page 5).
[93] Jacinta M Bonaventura et al. 'Reliability and accuracy of six hand-held blood lactate analysers'. In: Journal of sports science & medicine 14.1 (2015), p. 203 (cited on page 5).
[94] Robert Ahmun et al. 'Criterion validity of the lactate Pro LT-1710 portable analyser'. In: Journal of Sports Sciences 20.1 (2002), p. 31 (cited on page 5).
[95] Sachiko Ono, Gyohei Egawa, and Kenji Kabashima. 'Regulation of blood vascular permeability in the skin'. In: Inflammation and regeneration 37.1 (2017), pp. 1–8 (cited on page 6).
[96] John F Currie, Michael M Bodo, and Frederick J Pearce. Novel Non-Intrusive Trans-Dermal Remote Wireless Micro-Flui Tech. rep. Walter Reed Army Institute Of Research, 2004 (cited on page 6).
[97] PA Jansson, ANNE LENE Krogstad, and P Lonnroth. 'Microdialysis measurements in skin: evidence for significant lactate release in healthy humans'. In: American Journal of Physiology-Endocrinology And Metabolism 271.1 (1996), E138–E142 (cited on page 6).
[98] T Ohkuwa et al. 'The Relationship between Exercise Intensity and Lactate Concentration on the Skin Surface.' In: International Journal of Biomedical Science: IJBS 5.1 (2009), pp. 23–27 (cited on page 6).
[99] F Birklein, M Weber, and B Neundörfer. 'Increased skin lactate in complex regional pain syndrome: evidence for tissue hypoxia?' In: Neurology 55.8 (2000), pp. 1213–1215 (cited on page 6).
[100] M Muller et al. 'Measurement of interstitial muscle glucose and lactate concentrations during an oral glucose tolerance test'. In: American Journal of Physiology-Endocrinology And Metabolism 271.6 (1996), E1003–E1007 (cited on page 6).
[101] Röcker K Ahlgrim C Prettin S. 'Blood lactate levels at rest: Normal values and association with predominant type of exercise'. In: Berlin, Oct. 2012, pp. 7–8 (cited on page 6).
[102] Damien K Ming et al. 'Real-time continuous measurement of lactate through a minimally invasive microneedle patch: a phase I clinical study'. In: BMJ Innovations 8.2 (2022) (cited on page 6).
[103] Ming-Nan Chien et al. 'Continuous Lactate Monitoring System Based on Percutaneous Microneedle Array'. In: Sensors 22.4 (2022), p. 1468 (cited on page 6).
[104] Irwin M Braverman. 'The cutaneous microcirculation'. In: 5.1 (2000), pp. 3–9 (cited on page 6).
[105] AL Krogstad et al. 'Microdialysis methodology for the measurement of dermal interstitial fluid in humans'. In: British Journal of Dermatology 134.6 (1996), pp. 1005–1012 (cited on page 6).
[106] Anna-Maria Spehar-Délèze, Salzitsa Anastasova, and Pankaj Vadgama. 'Monitoring of lactate in interstitial fluid, saliva and sweat by electrochemical biosensor: the uncertainties of biological interpretation'. In: Chemosensors 9.8 (2021), p. 195 (cited on page 7).