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Development of an Implantable Biosensor for Real-Time Lactate Monitoring in Critically Ill Patients

Riis S[1*], Kovacic B[2] and Kazlauskas I[3]

[1]*Department of Biomedical Engineering, University of Copenhagen, Copenhagen, Denmark*
[2]*Department of Intensive Care Medicine, University of Ljubljana, Ljubljana, Slovenia*
[3]*Department of Analytical Chemistry, Lithuanian University of Health Sciences, Kaunas, Lithuania*

ABSTRACT

Background: Blood lactate is a well-established marker of tissue hypoperfusion and a validated resuscitation target in sepsis and septic shock, yet routine intensive care unit (ICU) practice still relies on intermittent arterial or venous blood gas sampling, leaving the dynamic, minute-to-minute behavior of lactate largely unobserved between draws. Objective: This narrative review synthesizes published literature on implantable and minimally invasive biosensors developed to enable continuous, real-time lactate monitoring in critically ill patients. Methods: We reviewed clinical, engineering, and physiological studies spanning the prognostic rationale for continuous lactate monitoring, enzymatic amperometric lactate oxidase sensor chemistry, and device architectures including percutaneous microneedle arrays, subcutaneous and intravenous catheter-based sensors, intravascular microdialysis, and fully bioresorbable deep-tissue implants. Findings: Trial-level evidence confirms that acting on serial lactate measurements improves survival in sepsis, and subcutaneous tissue lactate clearance has been shown to predict ICU non-survival independently of blood lactate. Intravascular microdialysis and intravenous catheter sensors currently achieve the closest agreement with arterial blood gas reference measurements and the fastest response times, while microneedle and bioresorbable platforms offer progressively less invasive alternatives that have been validated chiefly in animal models, with at least one microneedle-based system now evaluated directly in critically ill ICU patients. Conclusions: Continuous implantable lactate biosensors have progressed from proof-of-concept transducers to platforms undergoing early clinical evaluation in the ICU, and maturing wireless telemetry and multiplexed biomarker integration may position them as standard components of real-time metabolic monitoring in critical care.

Keywords: *implantable lactate biosensor; continuous lactate monitoring; critically ill patients; microneedle biosensor; sepsis resuscitation monitoring*

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Corresponding Author: *Soren Riis*

E-mail Address: *soren.riis@universityofcopenhagen.edu*

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Introduction

Elevated blood lactate has been recognized as a marker of tissue hypoperfusion and impaired oxidative metabolism for more than six decades, since Broder and Weil first demonstrated that an excess of lactate over its expected relationship with pyruvate tracked the reversibility of circulatory shock in human patients [1]. In contemporary critical care, lactate occupies a central place in the definition and management of sepsis and septic shock: the Third International Consensus Definitions (Sepsis-3) incorporate a serum lactate concentration above 2 mmol/L, in the presence of vasopressor-dependent hypotension, as part of the operational criteria for septic shock [2]. Beyond diagnosis, the trajectory of lactate over time carries substantial prognostic weight. Nguyen and colleagues showed that early lactate clearance during the initial hours of resuscitation for severe sepsis and septic shock was associated with improved survival, while Jansen and colleagues subsequently demonstrated in a multicenter randomized controlled trial that an explicit lactate-guided resuscitation protocol reduced hospital mortality in intensive care unit (ICU) patients from 43.5% in the control arm to 33.9% in the lactate-guided arm [3,4]. A systematic review by Vincent and colleagues subsequently consolidated this literature, concluding that both the absolute lactate level and its rate of clearance provide independent and complementary prognostic information in critically ill patients [5].

Despite this well-established clinical rationale, lactate monitoring in most ICUs remains fundamentally intermittent: values are obtained from arterial or venous blood gas samples drawn at

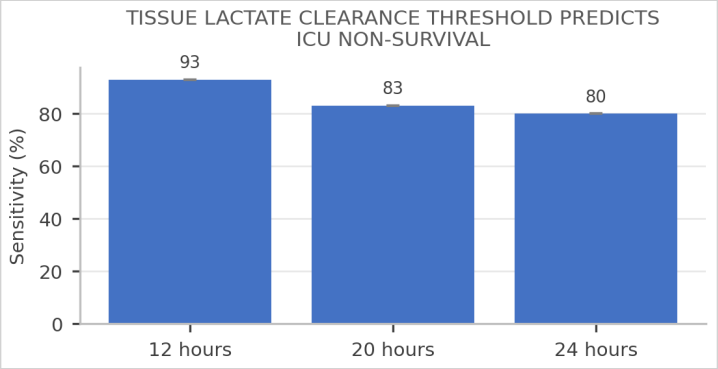
intervals of hours, providing only sparse snapshots of a metabolic signal that can change rapidly during evolving shock, resuscitation, or clinical deterioration. This mismatch between the dynamic nature of lactate kinetics and the discontinuous nature of laboratory sampling has motivated a substantial and rapidly growing body of engineering and clinical research aimed at continuous, minimally invasive or implantable lactate biosensing. This narrative review synthesizes that literature across four related domains: the physiological and clinical rationale for continuous rather than intermittent lactate monitoring in critical illness; the underlying sensor chemistry and transducer technologies, principally enzymatic amperometric platforms based on lactate oxidase; the specific device architectures—percutaneous microneedle, subcutaneous, intravascular, and fully implantable bioresorbable sensors—that have been engineered and tested for critical care application; and the clinical validation studies and telemetry considerations that determine translational readiness for real-time ICU deployment.

Lactate as a Physiological Signal in Critical Illness: Rationale for Continuous Monitoring

The physiological basis for lactate as a resuscitation target rests on its production during anaerobic glycolysis when tissue oxygen delivery fails to meet metabolic demand, a relationship first quantitatively linked to the reversibility of shock by Broder and Weil in their classic analysis of "excess lactate" in hypotensive human patients [1]. This foundational observation has been repeatedly reaffirmed in the sepsis literature: the Sepsis-3 consensus definitions formally embed an elevated lactate threshold within the diagnostic criteria for septic shock, reflecting international agreement that lactate elevation identifies a physiologically distinct, higher-risk subgroup of septic patients even in the presence of preserved blood pressure [2]. Clinically, the prognostic value of lactate is not limited to a single measurement but is substantially strengthened by its trend over time. Nguyen and colleagues, studying patients with severe sepsis and septic shock, found that patients whose lactate cleared more rapidly during early resuscitation had better outcomes than those with persistently elevated levels, establishing lactate clearance as an actionable resuscitation target rather than a static laboratory value [3]. This concept was tested prospectively by Jansen and colleagues in a multicenter, open-label, randomized controlled trial in which ICU patients with an admission lactate concentration above 3.0 mmol/L were randomized to a resuscitation protocol explicitly targeting a lactate decrease of at least 20% every two hours versus standard care; the lactate-guided strategy was associated with a reduction in hospital mortality from 43.5% to 33.9%, providing direct trial-level evidence that acting on serial lactate measurements can change clinical outcomes [4]. Vincent and colleagues' systematic review of blood lactate kinetics in critically ill patients synthesized this body of work and concluded that both single lactate values and clearance rates independently predict mortality across heterogeneous critically ill populations, reinforcing lactate's status as one of the few biomarkers with trial-level evidence linking its serial monitoring to a mortality benefit [5].

A parallel line of investigation has examined whether lactate measured in peripheral tissue, rather than in blood, might provide additional or even superior prognostic information, a question directly relevant to the design of implantable and subcutaneous continuous sensors. Ilias and colleagues used subcutaneous adipose tissue microdialysis in 111 ICU patients with sepsis or septic shock and found that tissue lactate clearance, but not blood lactate clearance, differed significantly between survivors and non-survivors; a tissue lactate clearance below 30% during the first 12, 20, and 24 hours of monitoring identified non-survivors with sensitivities of 93%, 83%, and 80% respectively, and remained an independent predictor of mortality in multivariate analysis with odds ratios of 4.2, 3.2, and 3.0 at these time points [6]. This finding is notable because it suggests that tissue-level lactate kinetics, of the kind captured by subcutaneous or interstitial biosensors, may carry prognostic information that is not fully redundant with intermittent blood lactate sampling—a central part of the rationale for developing continuous, tissue-embedded lactate biosensors rather than simply increasing the frequency of blood draws.

Sensitivity of a subcutaneous adipose tissue lactate clearance threshold (<30%) for predicting non-survival at 12, 20, and 24 hours after ICU admission in patients with sepsis or septic shock, illustrating the prognostic value of tissue-level lactate kinetics that motivates continuous interstitial sensing [6].



Sensor Chemistry and Transducer Design for Continuous Lactate Biosensing

The dominant sensing chemistry across the continuous lactate biosensor literature is enzymatic and amperometric, exploiting the enzyme lactate oxidase to catalyze the oxidation of L-lactate to pyruvate and hydrogen peroxide, with the peroxide product (or a mediated electron-transfer pathway) generating a current proportional to local lactate concentration at a working electrode. Ding and colleagues' comprehensive review of lactate biosensor materials traces this enzymatic architecture across generations of electrode design, from first-generation oxygen-dependent peroxide detection through second-generation mediator-based systems to third-generation direct electron transfer configurations, and catalogs the immobilization chemistries—including various hydrogels, conductive polymers, and nanomaterial composites—used to stabilize lactate oxidase on flexible or miniaturized electrodes [7]. Lafuente and colleagues' review of continuous and non-invasive lactate monitoring techniques in critical care patients similarly surveys enzymatic electrochemical platforms alongside optical and microdialysis-based alternatives, concluding that amperometric lactate oxidase sensors remain the most clinically mature approach for continuous bedside use owing to their fast response and compatibility with miniaturized, wearable, or catheter-based form factors [8].

Foundational work establishing the feasibility of flexible, skin-interfaced enzymatic lactate sensing outside the traditional benchtop laboratory includes the fully integrated wearable sensor array of Gao and colleagues, which combined a lactate oxidase-based amperometric electrode with glucose, sodium, and

potassium sensors together with signal-conditioning and wireless transmission electronics on a single flexible platform for multiplexed in situ analysis of human sweat [9]. Jia and colleagues developed an earlier printable electrochemical tattoo biosensor using a Prussian Blue-mediated lactate oxidase electrode for real-time, noninvasive lactate monitoring directly on the skin during physical exertion, demonstrating that flexible, epidermal enzymatic architectures could track lactate dynamics continuously outside a clinical laboratory [10]. While these sweat-based platforms were developed primarily for exercise physiology rather than critical care, they established core transducer and signal-processing principles—flexible substrates, mediator-based electron transfer, and integrated wireless readout—that have since been adapted toward interstitial, subcutaneous, and intravascular lactate sensing in hospitalized patients. A distinct engineering concern for any sensor intended for implantation, rather than epidermal contact, is the foreign body response: Wang and colleagues showed that the magnitude of local tissue trauma and the physical size of an implanted biosensor both significantly influence the intensity and duration of the ensuing foreign body reaction, which in turn degrades analyte diffusion to the sensing surface and drives long-term signal drift, a mechanistic consideration that directly shapes the miniaturized, minimally traumatic designs favored by current implantable lactate sensor platforms [11]. Extending sensor chemistry toward multiplexed and prognostically richer readouts, Nandhakumar and colleagues developed a bioelectronic platform capable of rapid, continuous, and simultaneous monitoring of both interleukin-6 and lactate from the same physiological compartment, explicitly targeting early sepsis prediction by combining a metabolic biomarker with an inflammatory one on a single sensing platform [12].

Implantable, Microneedle, and Intravascular Device Architectures for Critical Care

Translating enzymatic lactate sensing chemistry into a device suitable for continuous use in hospitalized or critically ill patients has followed several distinct architectural strategies, distinguished chiefly by anatomical compartment and degree of invasiveness. Percutaneous and intradermal microneedle arrays represent one prominent approach, minimizing pain and tissue trauma while accessing interstitial fluid at a shallow depth. Chien and colleagues developed a continuous lactate monitoring system based on a percutaneous microneedle array and validated it in 40 healthy adults undergoing incremental cycling exercise, reporting a measurement range of 5-360 mg/dL, a positive correlation between sensor output and blood lactate, and a practical device service life of approximately one month before sensitivity declined [13]. Wang and colleagues subsequently reported a more sensitive intradermal microneedle sensor patch, achieving a sensitivity of –8.04 nA per mM, a linear range spanning 0.25-35 mM, a 30-second response time, and a Pearson correlation of 0.85 with blood lactate reference values (after accounting for a roughly 10-minute physiological lag) in anesthetized rats, results the authors argued establish the platform's readiness for continuous physiological and clinical lactate monitoring [14].

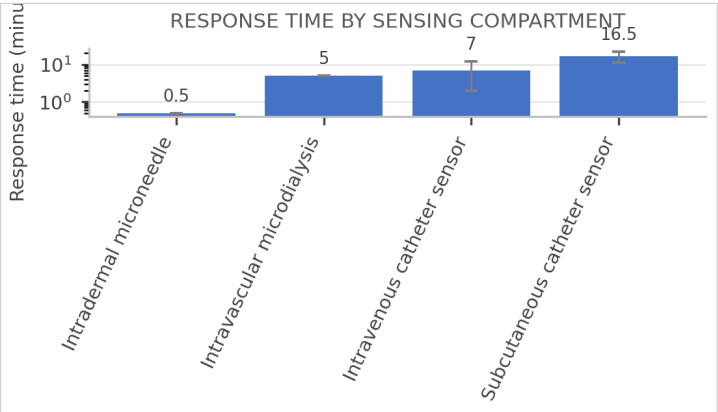
Deeper anatomical compartments have been targeted by intravenous, subcutaneous, and fully implantable sensor designs more directly relevant to hemodynamically unstable ICU patients. Wolf and colleagues compared intravenous and subcutaneous placements of a continuous electrochemical lactate sensor in a heparinized porcine model, finding that intravenously placed sensors achieved a mean absolute percentage error of 20% or better against a benchtop point-of-care reference, with response times of 2-12 minutes, whereas subcutaneously placed sensors were substantially less accurate, with three of four sensors showing 70-90% error and markedly slower response times of 11-22 minutes—directly demonstrating that intravascular placement confers a meaningful accuracy and speed advantage over subcutaneous sensing for critical care applications [15]. Schierenbeck and colleagues took a related but distinct approach, introducing intravascular microdialysis for continuous lactate monitoring in 80 patients undergoing cardiac surgery with cardiopulmonary bypass; across more than 1,600 paired samples, microdialysis-derived lactate correlated strongly with arterial blood gas lactate (regression coefficient 0.98), with a Bland-Altman bias of only 0.02 ± 0.42 mmol/L and an approximately five-minute lag time, and the authors further observed that a lactate elevation above 3.0 mmol/L was associated with postoperative complications [16]. At the most invasive end of the spectrum, Hu and colleagues developed a fully bioresorbable electrochemical sensor for continuous deep-tissue lactate monitoring, validated across rabbit, porcine, and rat models of systemic hypoxia, ischemia, epilepsy, and septic shock; the device maintained a linear response up to 30 mM lactate with a detection limit of 0.1 mM, remained functional for more than ten days in vivo, retained over 90% of its initial response after nine days of bench testing, and continued to track rising tissue lactate during physiological deterioration even when conventional vital signs such as pulse rate and oxygen saturation remained unchanged—directly illustrating the potential of a deep-tissue implantable sensor to detect metabolic compromise earlier than standard monitoring [17]. Most directly relevant to the translational question addressed by this review, Djassemi and colleagues recently reported a clinical evaluation of microneedle biosensors for continuous lactate monitoring specifically in critically ill patients, concluding that the platform is feasible for bedside deployment and holds considerable potential to transform sepsis care, guide resuscitation, and improve real-time assessment of physiological exertion and deterioration in the ICU setting [18]. Cai and colleagues' broader review of wearable and implantable biosensors for metabolic, hormonal, and inflammatory biomarkers situates these lactate-specific platforms within a wider translational movement toward continuous, multi-analyte physiological monitoring extending well beyond glucose, the historically dominant target of implantable biosensor research [19].

Representative implantable and minimally invasive continuous lactate biosensor platforms: sensing compartment, reported analytical performance, and validation stage.

Platform	Sensing compartment	Reported performance	Validation stage
Wang et al. intradermal microneedle [14]	Interstitial fluid (intradermal)	Sensitivity -8.04 nA/mM; linear range 0.25-35 mM; r=0.85 vs blood	Animal (rat), in vivo
Chien et al. percutaneous microneedle array [13]	Interstitial fluid (percutaneous)	Measurement range 5-360 mg/dL; service life ~1 month	Human, n=40, exercise study
Wolf et al. electrochemical catheter sensor [15]	Intravenous vs subcutaneous	MAPE <=20% (IV) vs 70-90% (subcutaneous)	Porcine, in vivo

Platform	Sensing compartment	Reported performance	Validation stage
Schierenbeck et al. intravascular microdialysis [16]	Central venous/arterial catheter	r=0.98 vs arterial blood gas; bias 0.02 +/- 0.42 mmol/L	Human, cardiac surgery, n=80
Hu et al. bioresorbable sensor [17]	Deep tissue (fully implanted)	Linear to 30 mM; detection limit 0.1 mM; functional >10 days	Animal (rabbit/porcine/rat), in vivo
Djassemi et al. microneedle biosensor [18]	Interstitial fluid, ICU patients	Feasibility for continuous ICU lactate trending demonstrated	Human, critically ill ICU patients

Representative response times reported for continuous lactate sensing platforms by anatomical compartment: intradermal microneedle sensing reaches steady-state within 30 seconds [14], intravascular microdialysis lags arterial blood by approximately 5 minutes [16], and intravenous versus subcutaneous electrochemical catheter sensors show midpoint response times of roughly 7 and 16.5 minutes respectively across their reported 2-12 and 11-22 minute ranges [15].



Clinical Validation, Telemetry, and Translational Outlook in the ICU

Continuous ambulatory or bedside operation of an implantable or minimally invasive lactate sensor depends on more than sensing chemistry alone; it requires power delivery, signal conditioning, and wireless data telemetry architectures compatible with the constraints of a hospitalized, often hemodynamically monitored patient. Kim and colleagues' review of wireless, batteryless, implantable electronics for real-time continuous physiological monitoring outlines the principal engineering strategies applicable to this problem, including inductive and radiofrequency power harvesting, resonant and impedance-based wireless readout, and increasingly sophisticated on-chip signal processing that allow implanted or percutaneous sensors to transmit continuous physiological data without requiring an onboard battery or a wired connection to bedside monitoring equipment [20]. These telemetry principles are directly applicable to the lactate sensor architectures described above: the wearable multiplexed sweat sensor array of Gao and colleagues integrated flexible signal-conditioning and wireless transmission circuitry alongside its lactate oxidase electrode from the outset [9], while more clinically oriented platforms such as the microneedle system of Djassemi and colleagues and the bioelectronic dual-analyte platform of Nandhakumar and colleagues are explicitly designed around continuous data streams intended for real-time clinical decision support rather than intermittent, retrospectively analyzed measurements [18,12].

Key clinical and preclinical studies linking lactate kinetics or continuous sensor output to outcomes and validation in critical illness.

Study	Population/design	Comparator	Principal finding
Nguyen et al. 2004 [3]	Emergency department patients, severe sepsis/septic shock	Serial blood lactate	Early lactate clearance associated with improved survival
Jansen et al. 2010 [4]	Multicenter RCT, ICU patients	Lactate-guided vs standard resuscitation	Hospital mortality reduced from 43.5% to 33.9%
Ilias et al. 2018 [6]	111 ICU patients, sepsis/septic shock	Adipose tissue microdialysis vs blood lactate	Tissue lactate clearance <30% predicted non-survival (sensitivity 93/83/80% at 12/20/24 h; OR 3.0-4.2)
Schierenbeck et al. 2014 [16]	80 cardiac surgery patients	Intravascular microdialysis vs arterial blood gas	r=0.98; bias 0.02 +/- 0.42 mmol/L; ~5 min lag
Djassemi et al. 2026 [18]	Critically ill ICU patients	Microneedle biosensor vs standard blood gas lactate	Established feasibility of continuous microneedle-based ICU lactate monitoring

Taken together, the clinical validation literature reviewed here supports a coherent translational narrative. Trial-level evidence from Nguyen and colleagues and Jansen and colleagues already establishes that acting on serial, even intermittently sampled, lactate measurements improves outcomes in sepsis and critical illness [3,4], while tissue-level microdialysis data from Ilias and colleagues suggest that continuous interstitial or subcutaneous lactate kinetics may add prognostic information beyond blood sampling alone [6]. Device-level validation studies converge on the conclusion that intravascular and intravenous placements, as in the work of Schierenbeck and colleagues and Wolf and colleagues, achieve the highest accuracy and fastest response relative to reference blood gas measurements, while microneedle and bioresorbable deep-tissue platforms from Wang and colleagues, Chien and colleagues, and Hu and colleagues offer progressively less invasive or fully implantable alternatives with encouraging but generally shorter-duration validation, mostly in animal models [16,15,14,13,17]. The recent clinical evaluation of a microneedle-based platform directly in critically ill ICU patients by Djassemi and colleagues represents an important step beyond animal validation toward real-world deployment [18], though the broader literature synthesized by Ding and colleagues, Lafuente and colleagues, and Cai and colleagues indicates that questions of long-term sensor stability, foreign body response as characterized by Wang and colleagues, and integration with hospital telemetry and electronic health record systems remain active areas requiring further clinical investigation before continuous implantable lactate biosensing can be considered standard ICU practice [7,8,19,11].

Conclusion

Lactate has been a cornerstone biomarker of tissue hypoperfusion and a validated target for resuscitation in critically ill patients

since the earliest descriptions of excess lactate in shock, with trial-level evidence directly linking serial lactate-guided care to improved survival [1,3,4,5]. The persistent gap between this well-established clinical rationale and the reality of sparse, intermittent blood gas sampling has driven a substantial engineering effort toward continuous lactate biosensing, built predominantly on enzymatic amperometric lactate oxidase chemistry and realized across an increasingly diverse set of device architectures spanning percutaneous microneedle arrays, subcutaneous and intravenous catheter-based sensors, intravascular microdialysis, and fully bioresorbable deep-tissue implants [7,8,13,14,15,16,17]. Preclinical and early clinical validation data indicate that intravascular placement currently offers the best accuracy and fastest response, that tissue-level lactate kinetics may carry prognostic information not fully captured by blood sampling alone, and that at least one microneedle-based platform has now been evaluated directly in critically ill ICU patients with encouraging feasibility [6,18]. As wireless, batteryless telemetry architectures mature and multiplexed platforms combining lactate with complementary biomarkers such as interleukin-6 move toward clinical testing, implantable and minimally invasive continuous lactate biosensors are well positioned to transition from proof-of-concept devices toward integrated components of real-time hemodynamic and metabolic monitoring in the intensive care unit [20,12,19].

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Riis S conceived the review, conducted the literature search and verification of cited sources, and drafted the manuscript. Kovacic B contributed clinical intensive care expertise, framed the physiological and prognostic significance of lactate monitoring, and critically revised the manuscript for important intellectual content. Kazlauskas I contributed analytical chemistry and biosensor engineering expertise, verified the sensor chemistry and device performance data presented, and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

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