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VENOUS VS. ARTERIAL BLOOD GAS INDICES FOR EARLY DETECTION OF SEPSIS: A LABORATORY PERSPECTIVE SYSTEMATIC REVIEW

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Abstract

Background: Early recognition of hypoperfusion in suspected sepsis is essential. Laboratory pathways and the sampling site (arterial vs venous) influence timeliness and interpretability of biomarkers. Objective: To synthesize evidence on venous blood gas (VBG) and arterial blood gas (ABG)–derived indices, mainly lactate and veno-arterial CO_2 differences, for early detection and monitoring of sepsis, emphasizing practical laboratory implications. Methods: We undertook a structured review of user-provided sources: pathophysiology/review papers and clinical studies. We extracted study design, setting, and key quantitative findings relevant to early detection, agreement between VBG and ABG lactate, and venous-to-arterial CO_2 metrics. Results: Bedside lactate point-of-care testing shortens turnaround without clear mortality benefit. Peripheral venous lactate ≤2 mmol/L safely rule out arterial hyperlactatemia with high sensitivity, supporting venous screening and selective ABG confirmation. Agreement studies show strong arterial–venous correlations but wide limits of agreement, cautioning against simple conversion. CO_2-gap–based indices ($Pv\text{-}aCO_2$; $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$) add prognostic/resuscitation context, though physiological caveats exist. Conclusions: For early detection, peripheral VBG lactate is an efficient screen; ABG is warranted when venous lactate >2 mmol/L or when precise gas exchange/acid-base data are needed. CO_2-gap indices can complement lactate to identify persistent hypoperfusion but require careful interpretation and standardized workflows.

Keywords: Sepsis; Lactate; Venous Blood Gas; Arterial Blood Gas; Point-of-Care Testing; $Pv\text{-}aCO_2$; $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$; Laboratory Turnaround Time.

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INTRODUCTION

Rapid laboratory confirmation of hyperlactatemia is central to sepsis bundles, arterial versus venous sampling and central laboratory versus point-of-care testing (POCT), directly affects time-to-decision and repeat-testing workflows. Implementing bedside lactate POCT in the emergency department (ED) reduce time-to-result and increase subsequent measurements, though without a demonstrable short-term mortality benefit (Lee et al. 2024). From a laboratory perspective, such time savings during crowding still be decisive for early escalation and bundle adherence.

Lactate participates in immunometabolic signaling via protein lactylation, linking metabolic flux to gene regulation in inflammation, supporting its prognostic salience in sepsis and motivating nuanced interpretation of elevated levels (Liu et al. 2024). This dual role, metabolite and epigenetic modifier, reinforces why early, repeated lactate measurements are meaningful for both diagnosis and trajectory (Ryoo and Kim 2018). Modern definitions and bundles embed lactate kinetics: the Sepsis-3 framework recognizes elevated lactate as defining severity in septic shock, and guidelines advocate prompt measurement with serial re-assessment and normalization strategies (Ryoo and Kim 2018).

Timely access to arterial lines is uneven in ED practice; efficient workflows commonly start with peripheral venous blood, escalating to ABG when clinical or numeric triggers demand. CO_2-based indices complement lactate, the central venous–arterial PCO_2 gap (Pcv-aCO_2) rises when cardiac output is low and may reflect global flow inadequacy; combining CO_2 and O_2 content differences (Pcv-aCO_2/Ca-cvO_2) has been proposed as a surrogate for respiratory quotient under oxygen-supply dependency (Dubin and Pozo 2023; Dubin et al. 2020). Yet physiological dependencies (CO_2–Hb dissociation, the Haldane effect, metabolic acidosis, hemodilution) complicate interpretation, and evidence quality is variable (Dubin and Pozo 2023; Dubin et al. 2020). This review synthesizes how VBG and ABG indices, especially lactate and CO_2-gap metrics, can be operationalized in laboratory pathways to enable earlier sepsis detection and smarter re-testing, drawing on recent implementation studies (POCT), pathophysiologic reviews (lactate/lactylation), and clinical research on CO_2-gap interpretation.

METHODOLOGY

We performed a structured synthesis of a predefined corpus focused on early laboratory detection and monitoring of sepsis. Sources comprised: (i) conceptual/physiologic and review articles supplied by the user and (ii) clinical/observational or analytic studies. Eligibility required addressing at least one of: agreement or correlation between venous and arterial lactate; diagnostic rule-out thresholds using venous lactate; prognostic or resuscitation roles of Pv-aCO_2 or Pcv-aCO_2/Ca-cvO_2 in sepsis; laboratory workflow or POCT effects on turnaround. Conceptual physiology papers were included to anchor interpretation (Sepsis-3 contextualization of lactate, immunometabolic roles, CO_2 physiology).

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We extracted sample characteristics, care setting, index tests (sampling site and method), and key quantitative outputs (correlation coefficients, mean differences and limits of agreement, sensitivity/specificity thresholds, and associations with outcomes or lactate trends). Risk of bias was appraised qualitatively because the set included narrative reviews, single-center cohorts, and non-randomized designs. We emphasize consistency, effect magnitudes, and physiologic coherence across studies and explicitly note confounders for CO_2-based metrics (shifts in the CO_2–Hb dissociation curve, Haldane effect, acidosis, hemodilution).

Synthesis is organized into: lactate agreement/threshold evidence to inform when VBG can replace or defer ABG; CO_2-gap metrics as adjuncts for persistent hypoperfusion despite initial goal attainment; and laboratory workflow considerations (POCT vs central lab) affecting time-to-decision.

RESULTS

A systematic synthesis of ED and ICU cohorts indicates that a peripheral venous lactate ≤2 mmol/L reliably excludes arterial hyperlactatemia, supporting a venous-first screen with selective ABG confirmation (van Tienhoven et al. 2019; Datta et al. 2016/2017; Samaraweera et al. 2017). In a prospective ED pilot (n=37), arterial and peripheral venous lactate were strongly correlated yet differed by =0.5 mmol/L on average, with wide 95% limits of agreement, too wide for simple substitution (Browning et al. 2014). A large ED cohort (n=304) reported a mean arterial–venous difference of =0.4 mmol/L with limits of agreement 0.4 to 1.2 mmol/L, reinforcing that while group-level agreement is acceptable, patient-level substitution is imperfect—especially at higher lactate (Datta et al. 2016/2017). ICU data similarly show strong correlations among arterial, peripheral venous, and central venous lactate (Velissaris et al. 2019) but advise caution for single-sample conversions. Additional ICU sepsis work found strong A–V correlation but poor agreement; a V-lactate threshold (≥3.5–4.5 mmol/L) predicted arterial hyperlactatemia, again favoring venous screening with ABG confirmation rather than formulaic conversion (Theerawit et al. 2018; Mahmoodpoor et al. 2020). Time-to-result and laboratory pathways: Introducing ED POCT lactate shortened time-to-result and increased repeat testing rates, supporting strategies that start with venous sampling on POCT analyzers to expedite triage, then escalate to ABG/central-lab as indicated (Lee et al. 2024). Pv-aCO_2 increases when blood flow is inadequate relative to CO_2 production; Pcv-aCO_2 approximates global flow. Combining CO_2 and O_2 content differences (Pcv-aCO_2/Ca-cvO_2) has been proposed as a surrogate of respiratory quotient during oxygen-supply dependency (Dubin and Pozo 2023; Dubin et al. 2020). In early septic shock, persistently high Pv-aCO_2 during the first hours was associated with worse organ failure trajectories and higher mortality; time-course analyses showed slower lactate decline in non-survivors (Ospina-Tascón et al. 2013). In another ICU cohort, the CO_2/O_2 content-difference ratio was associated with subsequent lactate evolution during hemodynamic resuscitation—suggesting these indices may identify ongoing hypoperfusion even when traditional goals (ScvO_2) appear met (Mesquida et al. 2015;

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Mallat et al. 2014). CO_2-gap metrics are affected by shifts in the CO_2–Hb dissociation curve, metabolic acidosis, hemodilution, and the Haldane effect; surrogacy for respiratory quotient is debated and fixed cutoffs should be applied cautiously (Dubin and Pozo 2023; Dubin et al. 2020).

Table 1: VBG vs ABG lactate in sepsis: agreement and screening thresholds

Study	Setting / n	Comparison	Key quantitative findings	Implication
Browning et al. 2014	ED sepsis, n=37	Arterial vs peripheral venous lactate	Mean A–V diff =0.54 mmol/L; 95% LOA roughly −0.1 to 1.2 mmol/L; strong correlation	Not interchangeable at patient level; use as screen
Datta et al. 2016/2017	ED sepsis, n=304	Arterial vs peripheral venous lactate	Mean diff =0.4 mmol/L; LOA =−0.4 to 1.2 mmol/L	Group agreement OK; confirm when high
Velissaris et al. 2019	ED/ICU	A vs PV vs CV lactate	Very high correlations among sites; small biases	Venous screening; ABG for precision
Theerawit et al. 2018	ICU sepsis	A vs V lactate	Strong correlation but poor agreement; V-lactate ≥3.5–4.5 predicts A-lactate ≥4	Use thresholds to trigger ABG
Mahmoodpoor et al. 2020	ICU septic shock, n=100	A vs V lactate; clearance	Strong correlation; arterial > venous by small bias; low clearance + high lactate predicted mortality	Trending and thresholds over conversion
Samaraweera et al. 2017	Pediatrics	Venous strategy	≤2 mmol/L venous effectively excludes arterial hyperlactatemia	Pediatric screening mirrors adult

Table 2: CO_2-gap–based indices during early resuscitation

Study	Marker	Main finding	Take-home
Ospina-Tascón et al. 2013	Pv-aCO_2 (and Pcv-aCO_2)	Persistently high gaps associated with higher SOFA and mortality; slower lactate decline	Unmasks occult hypoperfusion after initial resuscitation
Mallat et al. 2014	ΔPCO_2 dynamics	Normalization of ΔPCO_2 over first 6 h paralleled greater lactate decrease	Falling gap suggests improving perfusion
Mesquida et al. 2015 (X10)	Pcv-aCO_2/Ca-cvO_2 ratio	Higher ratio associated with subsequent lack of lactate improvement	Adjunct signal of supply-dependency
Diaztagle Fernández et al. 2017	Pv-aCO_2 (systematic review)	Links to mortality and lactate outcomes across 12 observational studies	Supportive but heterogeneous evidence base

DISCUSSION

From a laboratory vantage point, the earliest actionable step is rapid lactate measurement. ED implementation of lactate POCT cut turnaround and increased re-checks—key operational gains during periods of crowding—even though mortality and bundle adherence did not change (Lee et al. 2024). This aligns with the Sepsis-3 emphasis on immediate testing and serial monitoring and with lactate-guided or

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lactate-clearance-guided care (Ryoo and Kim 2018). Biologically, lactate is more than a hypoxia by-product. Its immunometabolic effects—particularly protein lactylation—may couple metabolic state to gene expression during sepsis, providing a mechanistic substrate for its prognostic value and for strategies targeting clearance rather than single snapshots (Liu et al. 2024). The clinical literature reinforces those elevations above =2 mmol/L deserve prompt reassessment and those trends (clearance) outperform single values for risk (Mahmoodpoor et al. 2020). Regarding sampling, evidence consistently supports peripheral venous lactate as a screening tool, particularly at the ≤2 mmol/L threshold, which effectively excludes arterial hyperlactatemia in adults and children (van Tienhoven et al. 2019; Samaraweera et al. 2017). However, strong correlations can mask wide limits of agreement, so ABG should confirm when venous lactate exceeds screening thresholds, when respiratory mechanics/acid–base assessment is essential, or when precision is critical at high lactate (Browning et al. 2014; Datta et al. 2016/2017; Theerawit et al. 2018; Velissaris et al. 2019).

CO_2-gap indices provide complementary context. Pv-aCO_2 and Pcv-aCO_2 can unmask systemic flow inadequacy after initial resuscitation; combined CO_2/O_2 ratios sometimes track lactate evolution or oxygen consumption responses (Ospina-Tascón et al. 2013; Mesquida et al. 2015; Mallat et al. 2014). Yet critical reviews advise caution: CO_2-gap metrics are influenced by CO_2–Hb dissociation, acidosis, hemodilution, and the Haldane effect, limiting their role as rigid targets or respiratory-quotient surrogates; fixed cut-offs are physiologically fragile (Dubin and Pozo 2023; Dubin et al. 2020). A pragmatic algorithm is therefore venous-first: immediate venous POCT lactate; if ≤2 mmol/L, defer ABG unless respiratory concerns; if >2 mmol/L, obtain ABG for confirmation/acid–base and consider CO_2-gap measures (preferably with central venous access) to identify ongoing hypoperfusion despite achieved macro-goals; repeat lactate guided by clinical change and bundle requirements. This integrates the speed of venous POCT with the depth of ABG and adjunct indices, consistent with guideline emphasis on serial assessment. Limitations: Our synthesis reflects the provided sources. Evidence for CO_2-gap ratios include narrative reviews and single-center cohorts; generalizability and optimal cutoffs remain unsettled. Incorporation of immunometabolic insights (lactylation) is evolving and should not replace clinically validated endpoints, but it contextualizes why lactate remains informative in sepsis physiology.

CONCLUSION

Early sepsis detection benefits from a venous-first laboratory strategy. Peripheral venous lactate, especially ≤2 mmol/L, safely rules out arterial hyperlactatemia and speeds triage via POCT; ABG should follow when venous lactate is elevated or when detailed gas/acid-base evaluation is needed.

CO_2-gap–derived indices (Pv-aCO_2; Pcv-aCO_2/Ca-cvO_2) can reveal persistent hypoperfusion and inform resuscitation alongside lactate, but require context-aware interpretation due to physiological confounders. Standardized sampling, rapid analytical pathways, and serial reassessment remain the laboratory pillars of timely sepsis care.

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