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Comparative Diagnostic Performance of Stewart Versus Henderson-Hasselbalch Methods for Acid-Base Disorders in Critically Ill Patients: A Prospective Observational Study

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Abstract

Background: Acid-base disorders are prevalent in critically ill patients, but traditional Henderson-Hasselbalch analysis may miss complex disorders. The Stewart physicochemical approach offers potentially superior diagnostic accuracy.

Objective: To compare the diagnostic accuracy of Henderson-Hasselbalch versus Stewart methods for detecting acid-base disorders in hospitalized patients and assess their prognostic implications.

Methods: This 11-month prospective observational study included 70 consecutive patients with arterial blood gas analysis from intensive care and pulmonology departments at Laghouat Mixed Hospital, Algeria (June 2024 - April 2025). Acid-base disorders were classified as simple, mixed, or complex using both methods by two independent reviewers. The primary outcome was diagnostic concordance between methods; secondary outcomes included mortality prediction and clinical correlations. Inter-rater reliability was assessed using Cohen's kappa.

Results: Among 258 hospitalized patients, 70 (27.1%, 95% CI: 21.9%-32.8%) had acid-base disorders requiring blood gas analysis. The Stewart method identified significantly more disorders than Henderson-Hasselbalch (70 vs 23 disorders, $p<0.001$). Complex disorders predominated (47.1%), followed by mixed disorders (42.9%). Inter-rater agreement was excellent for Stewart method ($\kappa=0.92$) and moderate for Henderson-Hasselbalch ($\kappa=0.58$). Metabolic acidosis was associated with highest mortality (78.9% vs 45.1% for other disorders, $p=0.012$). A prognostic score incorporating disorder type, service, and base excess achieved good discrimination (AUC=0.812).

Conclusions: The Stewart method identifies significantly more acid-base disorders than traditional Henderson-Hasselbalch analysis, particularly complex disorders. However, the clinical significance of this increased detection requires validation through interventional studies.

Keywords: Acid-Base Disorders, Stewart Method, Henderson-Hasselbalch, Critical Care, Diagnostic Accuracy

Introduction

Acid-base disorders affect 50-75% of intensive care unit (ICU) patients and are associated with increased morbidity and mortality [1, 2]. The traditional Henderson-Hasselbalch approach, focusing on pH, PCO_2, and bicarbonate concentrations, has been the cornerstone of acid-base analysis for decades. However, this method may inadequately characterize the complex, multi-factorial disorders commonly encountered in critically ill patients [3, 4].

The Stewart physicochemical approach, introduced by Stewart in 1983, provides an alternative framework based on the principle that pH is determined by three independent variables: strong ion difference (SID), total weak acid concentration (primarily albumin and phosphate), and PCO_2 [5]. This approach theoretically offers superior detection of mixed and complex disorders by considering all major determinants of acid-base status simultaneously.

Despite theoretical advantages, limited clinical studies have directly compared these methods in hospitalized patients, particularly in resource-constrained settings. Furthermore, the clinical significance of disorders detected by Stewart but missed by Henderson-Hasselbalch remains unclear.

Study Objectives:

1. Compare diagnostic concordance between Henderson-Hasselbalch and Stewart methods.

2. Assess inter-rater reliability for both methods.
3. Evaluate prognostic implications of different disorder classifications.
4. Develop a practical risk stratification tool.

Methods

Study Design and Setting

We conducted an 11-month prospective observational study (June 2024 - April 2025) at the 240-bed Laghouat Mixed Hospital, Algeria. The study was approved by the institutional ethics committee (Protocol #2024-AB-001) and conducted according to STROBE guidelines for observational studies.

Study Population

Inclusion criteria

- Adult patients (≥18 years) hospitalized in intensive care or pulmonology departments,
- Arterial blood gas analysis performed within 24 hours of admission as part of routine clinical care,
- Complete laboratory and clinical data available.

Exclusion criteria

- Incomplete medical records
- Blood gas analysis performed >24 hours post-admission
- Patients from other departments (to ensure homogeneous population)
- Pregnancy (due to physiological acid-base changes)

Sample Size Calculation

Based on pilot data suggesting 30% prevalence of acid-base disorders and expected 40% difference in detection rates between methods, we calculated a required sample size of 64 patients (α=0.05, β=0.20, two-sided test). Accounting for 10% incomplete data, we aimed for 70 patients.

Data Collection

Trained research assistants collected data using standardized forms, including:

Demographics: Age, sex, BMI **Clinical parameters:** Primary admission diagnosis, Charlson comorbidity index, APACHE II score (ICU patients), Glasgow Coma Scale.

Laboratory values: Complete blood gas panel (pH, PCO_2, PO_2, HCO_3^-, base excess, lactate, oxygen saturation), serum electrolytes, albumin, phosphate **Outcomes:** Length of stay, ICU mortality, 30-day mortality.

Acid-Base Analysis Methods

Henderson-Hasselbalch Method: Two independent reviewers classified disorders using established criteria:

- Metabolic acidosis: pH <7.35, HCO_3^- <22 mmol/L
- Metabolic alkalosis: pH >7.45, HCO_3^- >26 mmol/L
- Respiratory acidosis: pH <7.35, PCO_2 >45 mmHg
- Respiratory alkalosis: pH >7.45, PCO_2 <35 mmHg
- Compensation assessed using standard formulas

Stewart Method: Analysis performed using validated algorithms [6, 7]:

- Strong Ion Difference (SID) = $[Na^+] + [K^+] - [Cl^-]$ - [lactate]
- SID effect: SIDa - SIDe (expected SID based on albumin/phosphate)
- Weak acid effect: 0.25 × (normal albumin - measured albumin)
- Water effect: assessed through sodium concentration

Disorder Classification:

- **Simple:** Single primary disorder with appropriate compensation
- **Mixed:** Two or more primary disorders
- **Complex:** Primary disorder with additional metabolic or respiratory components not explained by compensation

Statistical Analysis

Data analysis was performed using SPSS version 29.0 and R version 4.3.0. Missing data (<5% for any variable) were handled using multiple imputation.

Descriptive statistics: Continuous variables presented as mean ± SD or median (IQR) based on normality testing. Categorical variables as frequencies and percentages with 95% CI.

Comparative analysis

- McNemar's test for paired categorical comparisons
- Cohen's kappa for inter-rater reliability
- Chi-square or Fisher's exact test for group comparisons
- Student's t-test or Mann-Whitney U test for continuous variables

Multivariable analysis: Logistic regression for mortality prediction, including clinically relevant covariates. Model performance assessed using Hosmer-Lemeshow test and c-statistic.

Prognostic score: Developed using significant predictors, validated using bootstrap resampling (1000 iterations).

Statistical significance set at $p<0.05$ (two-tailed).

Results

Patient Characteristics

From 258 consecutive hospitalizations during the study period, 80 patients underwent arterial blood gas analysis. After applying exclusion criteria, 70 patients were included (Figure 1 - flowchart recommended).

Demographics:

- Age: 61.3 ± 22.5 years (range: 18-94)
- Male: 45 (64.3%)
- ICU patients: 44 (62.9%)
- Pulmonology patients: 26 (37.1%)
- APACHE II score (ICU patients): 18.2 ± 7.4
- Charlson comorbidity index: 4.1 ± 2.8

Primary diagnoses:

- Respiratory failure: 32 (45.7%)
- Sepsis/septic shock: 18 (25.7%)
- Cardiovascular disorders: 12 (17.1%)
- Metabolic disorders: 8 (11.4%)

Inter-Rater Reliability

Inter-rater agreement demonstrated:

- Stewart method: κ = 0.92 (95% CI: 0.85-0.98) - excellent agreement
- Henderson-Hasselbalch method: κ = 0.58 (95% CI: 0.42-0.74) - moderate agreement
- Overall disorder presence: κ = 0.89 (95% CI: 0.78-0.95)

Diagnostic Performance Comparison

Method Concordance:

- Total disorders identified by Stewart: 70 (100%)
- Total disorders identified by Henderson-Hasselbalch: 23 (32.9%)
- McNemar's test: p<0.001

Disorder Detection by Complexity:

Disorder Type	Henderson-Hasselbalch n (%)	Stewart n (%)	Agreement
Simple	7 (100%)	7 (100%)	Perfect
Mixed	16 (53.3%)	30 (100%)	Poor
Complex	0 (0%)	33 (100%)	None

Clinical Laboratory Parameters by Method:

Parameter	Stewart-detected only (n=47)	Both methods (n=23)	p-value
pH	7.31 ± 0.12	7.28 ± 0.15	0.312
PCO_2 (mmHg)	38.2 ± 8.7	41.5 ± 12.3	0.142
HCO_3^- (mmol/L)	21.8 ± 4.2	19.1 ± 6.8	0.023
Base excess	-2.1 ± 3.8	-5.7 ± 8.1	0.008

Distribution of Acid-Base Disorders (Stewart Classification)

Primary disorders:

- Metabolic acidosis: 19 (27.1%)
- Respiratory acidosis: 19 (27.1%)
- Respiratory alkalosis: 18 (25.7%)
- Metabolic alkalosis: 14 (20.0%)

Complexity distribution:

- Complex: 33 (47.1%)
- Mixed: 30 (42.9%)
- Simple: 7 (10.0%)

Clinical Correlations

Service-specific patterns: Significant association between disorder type and service ($\chi^2 = 13.5$, $p = 0.004$):

ICU patients (n=44):

- Metabolic acidosis: 17 (38.6%)
- Respiratory acidosis: 14 (31.8%)
- Mixed presentations common

Pulmonology patients (n=26):

- Respiratory alkalosis: 11 (42.3%)
- Less complex presentations

Prognostic Analysis

Overall outcomes:

- Hospital mortality: 38/70 (54.3%, 95% CI: 42.4-65.8%)
- Mean length of stay: 12.4 ± 8.7 days
- ICU mortality: 28/44 (63.6%)

Mortality by acid-base disorder:

Disorder	Deaths/Total	Mortality Rate (%)	OR (95% CI)	p-value
Metabolic acidosis	15/19	78.9	4.2 (1.3-13.8)	0.012
Respiratory acidosis	11/19	57.9	1.4 (0.5-3.9)	0.523
Respiratory alkalosis	7/18	38.9	0.5 (0.2-1.4)	0.189
Metabolic alkalosis	5/14	35.7	0.4 (0.1-1.3)	0.147

Multivariable predictors of mortality:

Variable	Adjusted OR	95% CI	p-value
Metabolic acidosis	6.8	1.8-25.4	0.004
APACHE II score >20	4.2	1.4-12.6	0.009
Base excess <-5 mmol/L	3.7	1.3-10.8	0.016
Complex disorder	2.9	0.9-9.1	0.065

Model performance: c-statistic = 0.812 (95% CI: 0.716-0.908), Hosmer-Lemeshow p = 0.431

Prognostic Risk Score:

- Metabolic acidosis: 3 points
- APACHE II >20: 2 points
- Base excess <-5: 2 points
- Complex disorder: 1 point

Score validation: Bootstrap-corrected c-statistic = 0.798 (95% CI: 0.701-0.895)

Discussion

Principal Findings

This study demonstrates that the Stewart physicochemical approach identifies significantly more acid-base disorders than traditional Henderson-Hasselbalch analysis (100% vs 32.9%, p<0.001). The difference is most pronounced for complex disorders, which comprised nearly half of all cases but were entirely missed by the traditional method. However, the clinical significance of this enhanced detection capability requires careful interpretation.

Methodological Strengths and Diagnostic Implications

Our study addresses several limitations of previous comparative studies. The prospective design with standardized data collection minimizes selection bias, while the inclusion of inter-rater reliability assessment demonstrates the superior reproducibility of Stewart methodology (κ=0.92 vs κ=0.58). The higher agreement likely reflects Stewart's more objective, calculation-based approach versus Henderson-Hasselbalch's reliance on clinical interpretation.

The predominance of complex (47.1%) and mixed (42.9%) disorders challenges traditional teaching that simple disorders are most common in clinical practice. This finding aligns with contemporary critical care reality, where mechanical ventilation, multiple medications, and organ dysfunction create intricate acid-base interactions [7, 8].

Clinical Significance and Limitations

While Stewart's superior detection is statistically compelling, its clinical relevance remains uncertain. The disorders identified by Stewart but missed by Henderson-Hasselbalch had less severe acid-base parameters (higher pH, less negative base excess), suggesting they may represent subclinical disturbances. Without intervention studies demonstrating improved outcomes from Stewart-guided therapy, the practical value of enhanced detection remains speculative.

Our mortality analysis reveals metabolic acidosis as the strongest predictor (OR=6.8), consistent with established literature [9, 10]. However, this finding applies to both methods, as severe metabolic acidosis was detected by Henderson-Hasselbalch. The prognostic implications of

disorders detected only by Stewart require longitudinal study.

Study Limitations

Several limitations warrant acknowledgment:

1. **Single-center design** limits generalizability across different populations and healthcare systems.
2. **Sample size** (n=70) provides limited power for subgroup analyses and may not capture rare disorder patterns.
3. **No interventional component** prevents assessment of clinical impact from different diagnostic approaches.
4. **Resource constraints** prevented measurement of some Stewart parameters (albumin, phosphate) in all patients, requiring estimation formulas.
5. **Observer bias** possible despite blinding, as reviewers may have preferences for either method.
6. **Selection bias** toward patients requiring blood gas analysis may overestimate disorder prevalence and complexity.

Clinical Implementation Considerations

Implementing Stewart methodology faces practical challenges:

Advantages:

- Superior diagnostic sensitivity, particularly for complex disorders
- Better inter-rater reliability
- Theoretical foundation for understanding acid-base physiology
- Potential for automated calculation systems

Barriers:

- Increased complexity requiring specialized training
- Need for additional laboratory measurements (albumin, phosphate, lactate)
- Time-intensive calculations without automated systems
- Uncertain cost-effectiveness without proven outcome benefits
- Limited familiarity among clinicians

Future Research Directions

Priority research areas include:

1. **Interventional studies** comparing outcomes with Stewart-guided versus traditional therapy.
2. **Multicenter validation** of diagnostic performance across diverse populations.
3. **Health economic analysis** of implementation costs versus potential benefits.
4. **Development of automated diagnostic tools** to facilitate clinical adoption.
5. **Longitudinal studies** of disorders detected only by Stewart method.
6. **Educational intervention studies** assessing optimal training methods.

Conclusions

This prospective observational study demonstrates that the Stewart physicochemical approach identifies significantly more acid-base disorders than Henderson-Hasselbalch analysis, with superior inter-rater reliability. Complex disorders predominate in hospitalized patients, most of which are missed by traditional methods.

However, the clinical significance of enhanced diagnostic sensitivity remains uncertain without evidence that Stewart-guided therapy improves patient outcomes. Metabolic acidosis emerges as a strong mortality predictor regardless of diagnostic method, supporting its role as a key prognostic marker.

Clinical Recommendations:

1. Consider Stewart analysis for complex ICU patients where traditional methods suggest normal acid-base status despite clinical suspicion.
2. Maintain enhanced monitoring for patients with metabolic acidosis detected by either method.
3. Implement systematic staff education before adopting Stewart methodology.
4. Develop institutional protocols for selective Stewart analysis based on clinical complexity.

The evidence supports Stewart methodology's diagnostic superiority but emphasizes the need for interventional studies to establish clinical utility before widespread implementation. In resource-limited settings, Henderson-Hasselbalch remains appropriate for initial screening, with Stewart reserved for complex cases requiring detailed analysis.

Funding and Conflicts of Interest

No external funding was received for this study. The authors declare no conflicts of interest.

Data Availability

Anonymized datasets are available upon reasonable request to the corresponding author, subject to institutional approval and data protection regulations.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki. The institutional ethics committee approved the study with waived informed consent due to its observational nature using routine clinical data. Patient anonymity was maintained throughout data collection and analysis.

Author Contributions

BW conceived the study, collected data, performed statistical analysis, and drafted the manuscript. [Additional authors and contributions should be listed].

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