Diagnostic Accuracy of Blood Lactate-to-Pyruvate Molar Ratio in the Differential Diagnosis of Congenital Lactic Acidosis

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Background: Although the blood lactate-to-pyruvate (L:P) molar ratio is used to distinguish between pyruvate dehydrogenase deficiency (PDH-D) and other causes of congenital lactic acidosis (CLA), its diagnostic accuracy for differentiating between these 2 types of CLA has not been evaluated formally.

Methods: We conducted a retrospective study of all patients followed for mitochondrial diseases between 1985 and 2005 in a tertiary care pediatric hospital.

Results: At the recommended cut point of 25, individual median L:P ratio demonstrated low sensitivity and specificity (77% and 91%, respectively) for differentiating between patients with enzymatically proven PDH-D (n = 11) and those with mitochondrial disease but normal pyruvate dehydrogenase (PDH) activity (non-PDH; n = 35). We observed a strong positive association between L:P ratio and blood lactate in non-PDH CLA, whereas this association was weak in PDH-D CLA. Consequently, patient classification based on median L:P ratio showed improved diagnostic accuracy at higher lactate concentrations: for lactate <2.5 mmol/L the area under the ROC curve was not statistically different from 0.5 (P = 0.3), whereas it was statistically different for lactate >2.5 mmol/L. In the 2.5 to 5.0 mmol/L lactate category, the sensitivity and specificity at an optimal cut point of 18.4 were 93% (95% CI, 77%–99%) and 71% (95% CI, 59%–100%), respectively. For lactate >5.0 mmol/L, with an optimal cut point of 25.8, sensitivity and specificity were 96% (95% CI, 77%–99%) and 100% (95% CI, 59%–100%), respectively.

Conclusion: Usefulness of the L:P ratio for differentiating non-PDH and PDH-D types of CLA increases at higher lactate concentrations.

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The blood lactate-to-pyruvate (L:P) molar ratio reflects the equilibrium between product and substrate of the reaction catalyzed by lactate dehydrogenase. The L:P ratio is correlated with the cytoplasmic NADH:NAD+ ratio and is used as a surrogate measure of the cytosolic oxido-reduction state (1). When cellular respiration is impaired, as in hypoxia, pyruvate oxidation is reduced, resulting in lactic acidosis. In such situations, reduced forms of oxido-reduction coenzymes (NADH, FADH2) predominate and L:P ratio is increased. A similar impairment of the oxidative metabolism occurs in inborn errors of the mitochondrial respiratory chain. In contrast, in pyruvate dehydrogenase deficiency (PDH-D), the metabolic block is upstream of the respiratory chain, and thus the cytoplasmic oxido-reduction state is predicted to be unaltered and the L:P ratio is normal or low (1, 2). Usually, an L:P molar ratio >25 is considered increased and suggestive of a primary (or secondary) respiratory chain dysfunction, whereas a ratio <25 is thought to be consistent with PDH-D (1). The usefulness of this cut point to correctly classify patients into primary respiratory chain dysfunction and PDH-D has not been evaluated, however. Moreover, other thresholds have been suggested (2-4). Rapid distinction between PDH-D and non-PDH CLA is needed in the emergent setting and for timely management.
respiratory chain diseases is desirable because there are specific treatments for PDH-D (5–7).

The objectives of our retrospective study were (a) to describe the distribution of L:P ratio in a cohort of pediatric patients with PDH-D and other causes of congenital lactic acidosis (CLA), (b) to examine the relationships between L:P ratio and lactate concentration according to the diagnostic group, and (c) to evaluate the diagnostic accuracy of the L:P ratio for differentiating between PDH-D and other causes of CLA.

Materials and Methods

Patients

Using a local database, we identified patients followed for mitochondrial disease or CLA at Ste-Justine Hospital, Montreal, Quebec, Canada, between 1985 and 2005. Inclusion criteria were evidence of a mitochondrial disorder according to the modified Walker scoring system (8) and available laboratory data for at least 1 increased lactate concentration and 1 simultaneous measurement of blood lactate and pyruvate. According to the Walker criteria, a diagnosis of mitochondrial disorder is made when the activity of a specific enzyme/respiratory chain complex is <30% in 1 cell line, <20% in 1 tissue, or <30% for the same enzyme/respiratory chain complex in 2 or more tissues (8). Enzymatic studies were performed at the Metabolism Research Program, Hospital for Sick Children, Toronto, Ontario, Canada (B.H. Robinson). Because of a genetic founder effect, patients with the Sagenay–Lac-St-Jean form of cytochrome c oxidase deficiency (MIM 220111) make up a large proportion (~25%) of our cases (9). We chose to exclude these patients to make our study population more similar to other groups of patients diagnosed with CLA elsewhere in the world. Case patients were divided in 2 groups. The PDH-D group (n = 11) included patients with enzymatically confirmed PDH-D in cultured skin fibroblasts. The mitochondrial group with normal pyruvate dehydrogenase (PDH) activity (non-PDH) comprised patients (n = 35) with confirmed respiratory chain deficiencies and patients with classical mitochondrial syndromes such as mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS), Kearns–Sayre, or mitochondrial myopathy with ragged red fibers. In this group, a biochemical defect was documented in 21 patients: complex IV deficiency, n = 8; complex I deficiency, n = 5; complex II + III deficiency, n = 2; multiple complexes deficiency, n = 5; pyruvate carboxylase deficiency (type B), n = 1. Eight patients had molecularly confirmed mitochondrial DNA (mtDNA) mutations: A3243G (MELAS), n = 4; deletion (Kearns–Sayre), n = 1; T8993G/C [neurogenic weakness, ataxia, retinitis pigmentosa (NARP)], n = 3. The remaining 6 patients in the non-PDH group had presentation compatible with classical mitochondrial syndromes: mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), n = 1; mitochondrial myopathy with ragged red fibers, n = 2] or clinical evidence of mitochondrial and/or respiratory chain dysfunction without enzymatic diagnosis (n = 3). All patients without molecular or biochemical diagnoses that were classified as non-PDH CLA had normal PDH activity in cultured skin fibroblasts.

The medical charts of all patients were retrospectively reviewed. All lactate and pyruvate concentrations from blood samples collected simultaneously were included in the data analyses. The median number of simultaneous tests per patient was 7 (range, 1–36).

Biochemical Analyses

Venous blood was obtained by venipuncture or through an indwelling catheter. When possible, no tourniquet was used. For lactate measurement, blood was collected in sodium fluoride tubes. For pyruvate determination, blood was precipitated at bedside with perchloric acid. Both tests were performed in the Clinical Biochemistry Laboratory at Ste-Justine Hospital. Over the course of this study, lactate was measured with Beckman Coulter analyzers by an end-point enzymatic reaction. In 2005, the analytical CVs at 1.10, 3.70, and 5.03 mmol/L were 3.8%, 2.5%, and 2.3%, respectively. Pyruvate was measured manually by an end-point enzymatic assay with lactate dehydrogenase and oxidation of NADH to NAD+. In 2005, the analytical CV at 0.17 mmol/L was 4.4%.

Statistical Analyses

A t-test for independent groups was used to compare means of individual median values for lactate and pyruvate concentrations and L:P ratio between diagnostic groups (PDH-D vs non-PDH). Hierarchical maximum likelihood linear regression was used to examine the association between L:P ratio (dependent variable) and lactate concentration and diagnostic group (explanatory variables). Explanatory variables were treated as fixed effects, and clustering within each individual was treated as a random effect (414 sets of measurements clustered within 46 individuals). We used a product term (lactate × diagnostic group; PDH-D group = reference group) to test whether the magnitude of the effect of the lactate concentration on L:P ratio varied as a function of the diagnostic category. Regression analysis was adjusted for sex and age at blood draw. ROC analysis was used to assess the diagnostic accuracy of the L:P ratio for differentiating between patients with PDH-D and patients with non-PDH-D forms of CLA. In ROC analyses we used the median value of L:P ratio for each individual as a summary measure of the repeated measurements (for all cases analyzed together or for cases within each specific lactate category). Statistical analyses were performed with SAS statistical software, version 8.2 (SAS Institute) with the exception of ROC analyses, which were performed with MedCalc software (Mariakerke) (10).

Results

Clinical and biochemical characteristics of patients are presented in Table 1 in the Data Supplement that accom-
panies the online version of this article at http://www.clinchem.org/content/vol53/issue5. A total of 414 simultaneous measurements of lactate and pyruvate were available for the study (276 in the non-PDH group and 138 in the PDH-D group); 52% (24/46) of patients had at least 1 lactate concentration <2.2 mmol/L, the upper limit of the reference range. In the non-PDH group, the median (range) of intraindividual CVs for lactate and pyruvate concentrations and L:P ratio were 35% (14%–75%), 25% (12%–61%), and 29% (6%–54%), respectively. The corresponding values in the PDH-D group were 21% (9%–59%), 29% (10%–68%), and 22% (12%–43%), respectively.

Means of individual median values for lactate and pyruvate concentrations were similar in the non-PDH and PDH-D groups (Table 1). Although means of individual median values for L:P ratio were statistically different between both groups ($P < 0.0001$), there was an important overlap of individual median values between the non-PDH and PDH-D groups. This characteristic limits the usefulness of the L:P ratio for distinguishing between patients with non-PDH and PDH-D forms of CLA.

### Table 1. Blood lactate and pyruvate median concentrations in patients with non-PDH and PDH-D forms of congenital lactic acidosis.

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Lactate, mmol/L*</th>
<th>Pyruvate, mmol/L*</th>
<th>L:P molar ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Non-PDH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys (n = 19)</td>
<td>5.15 (3.33)</td>
<td>1.5–14.1</td>
<td>0.154 (0.038)</td>
</tr>
<tr>
<td>Girls (n = 16)</td>
<td>4.48 (2.87)</td>
<td>1.8–11.4</td>
<td>0.143 (0.052)</td>
</tr>
<tr>
<td>Total (n = 35)</td>
<td>4.86 (3.11)</td>
<td>1.5–14.1</td>
<td>0.149 (0.044)</td>
</tr>
</tbody>
</table>

| PDH-D            |                 |                  |                 |                  |                 |                  |
| Boys (n = 6)     | 3.20 (2.46)     | 1.1–8.0          | 0.180 (0.164)   | 0.054–0.495      | 20.4 (6.3)      | 15.0–31.3        |
| Girls (n = 5)    | 5.28 (2.87)     | 3.2–10.2         | 0.284 (0.127)   | 0.138–0.486      | 18.1 (3.7)      | 13.6–23.3        |
| Total (n = 11)   | 4.15 (2.74)     | 1.1–10.2         | 0.227 (0.151)   | 0.054–0.495      | 19.4 (5.2)      | 13.6–31.3        |

$P$ value

| $P$ value $b$   | $<0.0001$       | $<0.0001$        |

* For each diagnostic group, by sex and both sexes combined, values are mean, SD, and range of individual median values for lactate and pyruvate concentrations and L:P ratio.

$P$ value for comparisons between non-PDH and PDH-D groups (both sexes combined).

### Relationships between L:P ratio, lactate concentration, and diagnostic group

Scatter plots of L:P ratio against lactate concentration showed a strong positive association between these 2 variables in the non-PDH group, whereas this association was weak in the PDH-D group (Fig. 1). As indicated by the highly significant interaction between lactate concentration and diagnostic group (Table 2), the magnitude of the effect of the lactate concentration on L:P ratio varied significantly as a function of the diagnostic group. After adjustment for sex and age at blood draw, we found that for each unit (1 mmol/L) increase in lactate, the difference in L:P ratio between non-PDH and PDH-D groups increased by 2.8 units ($P < 0.0001$). This observation suggested that the diagnostic accuracy of the L:P ratio for correctly classifying patients into primary respiratory chain dysfunctions (non-PDH) and PDH-D would improve as lactate concentration increased. To test this hypothesis we performed ROC analyses with the whole set of cases and after grouping the observations according to the lactate concentration.

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**Fig. 1.** Scatter plot of L:P ratio vs lactate concentration in patients with CLA.

- [ ] Non-PDH group; [ ] PDH-D group. The solid line represents the regression line for the PDH-D group, and the dashed line represents the regression line for the non-PDH group.
The regression coefficient; Ref, reference group.

Lactate is the slope for the PDH-D group (0.44); β for lactate is the slope for the PDH-D group (0.44); β for lactate + β for the interaction term lactate · non-PDH is the slope for the non-PDH group (0.44 + 2.82 = 3.26).

Table 2. Mixed multiple regression analysis showing the association between L:P ratio and lactate concentration and diagnostic group.

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>β*</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate, mmol/L†</td>
<td>0.44</td>
<td>0.40</td>
<td>0.278</td>
</tr>
<tr>
<td>Diagnostic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-PDH‡</td>
<td>-2.72</td>
<td>2.47</td>
<td>0.273</td>
</tr>
<tr>
<td>PDH-D</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate · non-PDH§</td>
<td>2.82</td>
<td>0.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lactate · PDH-D</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Regression model is adjusted for sex and age at blood draw.

† β indicates regression coefficient; SE, standard error; P, probability value for the regression coefficient; Ref, reference group.

‡ Regression coefficient (β) represents the change in mean L:P ratio per unit (1 mmol/L) increase in lactate after adjustment for all the other variables in the model.

§ Regression coefficient (β) represents the change in mean L:P ratio for the patients in the non-PDH group compared to those in the PDH-D reference group.

¶ Regression coefficient (β) represents the change in mean L:P ratio per unit (1 mmol/L) increase in lactate for the patients in non-PDH group compared with those in the PDH-D reference group and after adjustment for all other variables in the model. Slopes for each group can be easily obtained: β for lactate is the slope for the PDH-D group (0.44; β for lactate + β for the interaction term lactate · non-PDH is the slope for the non-PDH group (0.44 + 2.82 = 3.26).

ABILITY OF L:P RATIO TO DISTINGUISH BETWEEN NON-PDH AND PDH-D CLA ACCORDING TO LACTATE CATEGORY

ROC analysis of the whole group of patients showed that the optimal individual median L:P ratio threshold to distinguish between non-PDH and PDH-D individuals was 23.3 (Table 3). The sensitivity and specificity of this cut point to correctly identify individuals in the non-PDH group were 77% (95% CI, 60%–90%) and 91% (95% CI, 59%–99%), respectively.

We then divided observations according to 3 lactate concentration categories: <2.5 mmol/L, between 2.5 and 5.0 mmol/L, and >5.0 mmol/L. Within each category, for each individual, we used as a summary measure of the repeated L:P measurements his/her median L:P ratio value in the lactate category being considered. One individual could belong to more than 1 category as long as he/she had lactate concentration values within the limits of the category considered at some point during his/her follow-up. In fact, 86% of patients had lactate concentrations in more than 1 category, indicating that the metabolic status of patients varied widely over time. When lactate concentrations were <2.5 mmol/L, the area under the ROC curve was not statistically different from 0.5 (P = 0.3), suggesting that individual median L:P ratio in this category did not enable us to distinguish between patients with primary respiratory chain dysfunctions (non-PDH) and those with PDH-D (Table 3). When lactate was >2.5 mmol/L (2.5–4.99 and ≥5.0 categories), the individual median L:P ratio was useful in differentiating the 2 groups (P for area under the ROC curve <0.0001 for both categories; Table 3). The optimal cut point for the 2.5–4.99 mmol/L lactate category was 14.8 with a sensitivity and specificity of 95% to correctly identify individuals in the non-PDH group of 93% (95% CI, 77%–99%) and 71% (95% CI, 20%–96%), respectively. The optimal cut point for the ≥5.0 mmol/L lactate category was 25.8. Within this category, the sensitivity and specificity of the optimal cut point reached 96% (95% CI, 77%–99%) and 100% (95% CI, 59%–100%), respectively.

Table 3. Ability of L:P ratio to distinguish between patients with non-PDH and PDH-D forms of congenital lactic acidosis: ROC analysis.

<table>
<thead>
<tr>
<th>Lactate category</th>
<th>Estimate, 95% CI</th>
<th>P</th>
<th>Optimal cut point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cases§</td>
<td>0.83 (0.70–0.80)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.5§</td>
<td>0.62 (0.41–0.78)</td>
<td>0.3</td>
<td>&gt;18.4</td>
</tr>
<tr>
<td>2.5–4.99§</td>
<td>0.86 (0.70–0.95)</td>
<td>&lt;0.0001</td>
<td>92.9 (76.5–98.9)</td>
</tr>
<tr>
<td>−5.0§</td>
<td>0.99 (0.87–1.00)</td>
<td>&lt;0.0001</td>
<td>&gt;25.8</td>
</tr>
</tbody>
</table>

AUC: area under the curve.

Number of patients: non-PDH, 25; PDH-D, 11.

Number of patients: non-PDH, 28; PDH-D, 7.

Number of patients: non-PDH, 22; PDH-D, 7.

Discussion

CLA encompasses a broad group of inherited disorders of energy metabolism caused by defects of mitochondrial enzymes, including PDH and the respiratory chain complexes. The megacomplexes of oxidative phosphorylation contain dozens of subunits, each encoded either in the mitochondrial or nuclear genomes. Thus, mutations in either genome can cause respiratory chain defects (11).

The phenotypic expression of mitochondrial diseases caused by mtDNA mutations is influenced by heteroplasmy, particularly in tRNA defects and mtDNA deletions. For respiratory chain defects caused by nuclear gene’s mutations, similar tissue variability also occurs, but it occurs through mechanisms that are essentially unknown. Because of these organ-specific expression patterns, diagnosis of mitochondrial diseases often requires
analysis of deep tissues (12). Indeed, in most cases, diagnosis of respiratory chain defects is made by analysis of muscle and/or liver tissue(s). Muscle and liver biopsies are invasive procedures with adverse side effects. In contrast to respiratory chain defects, PDH-D shows a uniform tissue expression pattern and is easily diagnosed in cultured skin fibroblasts (1, 13), a far less invasive technique. Clinical distinction between respiratory chain defects and PDH-D is important to optimize the diagnostic work-up of these rare hereditary diseases but is frequently challenging. The L:P ratio is considered a useful clue to the correct diagnosis. Importantly, contrary to most other forms of CLA, PDH deficient patients can benefit from specific treatments (dichloroacetate, thiamine, ketogenic diet) (5–7). Thus, this diagnosis must be considered as soon as possible. The definitive confirmation of a PDH-D (or other mitochondrial diseases) remains the demonstration of deficient enzyme activity in the appropriate tissue or the identification of the causative mutation(s).

In our cohort, ROC analysis of individual median L:P ratio irrespective of the lactate category showed an optimal cut point at 23.3, which was close to the threshold of 25 commonly suggested in the literature to distinguish between PDH-D and other forms of CLA (1). However, the sensitivity of this cut point (23.3) to correctly classify patients as having non-PDH forms of CLA was only 77% (95% CI, 60%–90%).

The positive association between L:P ratio and lactate concentration was much stronger in respiratory chain deficiencies than in PDH-D. This notion, which was not previously reported, is intuitively appealing. From a pathophysiological standpoint, in periods of increased oxidative demand, respiratory chain deficiency would result in increased pyruvate concentrations and also a progressive increase of the cytoplasmic NADH:NAD⁺ ratio. Therefore, the L:P ratio is expected to increase along with lactate (or pyruvate) concentration. Moreover, depletion of ATP and increased ADP:ATP ratio inhibits PDH kinase, increasing PDH activity and NADH production. In contrast, in PDH-D, the NADH:NAD⁺ ratio should be unchanged even at high pyruvate concentrations, and the L:P ratio is expected to vary little with increases in blood lactate or pyruvate concentrations. Overall, these data suggest that L:P ratio should be interpreted according to the lactate concentration and that the diagnostic accuracy of the L:P ratio for distinguishing between non-PDH and PDH-D forms of CLA should improve with increasing lactate concentrations. This hypothesis was strongly supported by our data; the sensitivity and specificity of the optimal median L:P ratio cut point progressively improved across increasing lactate categories. It is of note that 86% of our patients had lactate concentrations in more than 1 lactate category. In practice, for a given patient, clinicians can be more confident in using the L:P ratio to differentiate between non-PDH and PDH-D forms of CLA when concentrations of lactate are higher. For lactate concentrations <2.5 mmol/L, L:P ratios did not show statistically significant differences between non-PDH and PDH-D forms of CLA. When lactate concentrations were between 2.5 and 4.99 mmol/L, specificity of the L:P ratio for distinguishing between non-PDH and PDH-D forms of CLA was only 71% (95% CI, 20%–95%). For lactate concentrations >5 mmol/L, diagnostic accuracy of the L:P ratio improved notably: sensitivity and specificity were 96% (95% CI, 77%–99%) and 100% (95% CI, 59%–100%), respectively.

Intraindividual variation in lactate and pyruvate concentrations was much higher in our group of patients than that previously described in controls (14), suggesting that their metabolic status was variable. Many (52%) had occasional blood lactate concentrations within the reference interval, indicating that blood lactate concentrations within the reference interval do not exclude a diagnosis of mitochondrial disease. The proportion of patients with occasional normal lactate concentrations was not statistically different between non-PDH and PDH-D groups (48% and 63%, respectively; \( P = 0.6 \)). Moreover, the mean (SD) percentage of increased lactate concentrations was similar in both groups [80% (29%) and 72% (34%) for the non-PDH and PDH-D groups, respectively; \( P = 0.5 \)].

Limitations of this study include its use of a retrospective design over a long period of time, which did not allow for planned and uniform quality control of preanalytical and analytical conditions for lactate and pyruvate measurements. Pyruvate is known to be more sensitive to preanalytical conditions than lactate (15), and suboptimal sampling conditions can result in L:P ratios that are artifactualy increased and may lead to increased estimates of the optimal L:P cut point for distinguishing between non-PDH and PDH-D forms of CLA. Nonetheless, in our group of patients analyzed as a whole, the optimal L:P ratio threshold (23.3) was similar to that suggested in the literature (1). Moreover, if L:P ratios were artifactualy increased, this effect should be nondifferential and similarly affect both groups of patients (non-PDH and PDH-D cases). Therefore, this effect does not invalidate our conclusion that the diagnostic accuracy of the L:P ratio for distinguishing between non-PDH and PDH-D forms of CLA improves with increasing lactate concentrations. To avoid overrepresentation of some individuals in ROC analyses, we used the median value of L:P ratio for each individual as a summary measure of the repeated measurements. The sensitivity and specificity of a single L:P ratio is expected to be decreased compared with that of the individual median L:P ratio. However, when we applied the L:P ratio cutoff of 25.8 and used only the 1st lactate and pyruvate measurements at presentation in patients with initial lactate concentrations >5 mmol/L (\( n = 22; 18 \) non-PDH and 4 PDH-D), we calculated a sensitivity of 94% and a specificity of 100% for distinguishing non-PDH from PDH-D forms of CLA. A further limitation of this study is its small sample size (46 patients). To our knowledge, however, this is the 1st
systematic evaluation of the accuracy of L:P ratio to differentiate between non-PDH and PDH-D forms of CLA.

In summary, there was a strong positive association between L:P ratio and blood lactate in non-PDH CLA, whereas this association was weak in PDH-D CLA. Consequently, the diagnostic accuracy of the L:P ratio for differentiating between non-PDH and PDH-D forms of CLA increased at higher lactate concentrations. These characteristics should be considered when clinicians use this indicator in the differential diagnosis of CLA.

Grant/funding support: None declared.
Financial disclosures: None declared.

References