The Metabolism of Lactate and Pyruvate in Children with Congenital Heart Disease

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with the technical assistance of Katharine S. Gullixson

Venous blood lactic acid and pyruvic acid concentrations and lactate-pyruvate ratio were studied in 42 normal adults, 16 normal children and 18 children with congenital heart disease. There was elevation of resting values in children as compared with adults, but no significant change of values of resting children with congenital heart disease as compared with normal children. Following a standard exercise test, children with patent ductus arteriosus showed a time curve comparable to normal children, but children with cyanotic heart disease showed a persisting elevation of all values. The lactate-pyruvate ratio varied inversely with calculated mean capillary blood PO₂.

Patients with congenital heart disease should be excellent subjects for evaluation of the metabolic effects of chronic hypoxemia. Direct measurements of the arterial blood oxygen tension of 30 individuals with tetralogy of Fallot show a range of 30.2 to 66.0 mm. Hg values significantly lower than recently reported arterial PO₂ figures for normal individuals. Although the work of Bing and associates would indicate that certain mechanisms reduce the gradient of fall between arterial blood PO₂ and mean capillary blood PO₂, the application of the formula of Barcroft for the approximation of “mean capillary PO₂” to Bing’s crude data shows a significant reduction of mean capillary blood PO₂ of the cyanotic patients in Bing’s series as compared with normal individuals. Such a reduction provides sufficient stimulus to the tissues to produce an increased concentration of hemoglobin in the circulating blood. The question arises whether or not such chronic hypoxemia results in alteration of mechanisms other than the oxyhemoglobin transport system.

One of the most noticeable accompaniments of acute hypoxia is the accumulation of lactic acid in the blood. Energy for the synthesis of high energy phosphate bonds during the glycolytic phase of carbohydrate breakdown is supplied largely by the reactions involved between 1,3-diphosphoglyceraldehyde and pyruvic acid. During the conversion of 1,3-diphosphoglyceraldehyde to 1,3-diphosphoglyceric acid, diphosphopyridine nucleotide (coenzyme I) is reduced, and to maintain the conversion adequate amounts of the oxidized nucleotide must be provided continually. In the presence of sufficient amounts of oxygen, the reduced diphosphopyridine nucleotide formed in this reaction is reoxidized through the cytochrome system. In the absence of adequate oxygen concentrations reoxidation is accomplished by pyruvic acid, the latter being reduced to lactic acid. The ratio of the concentrations of lactate and pyruvate in the circulating blood reflects the degrees to which the reoxidation of diphosphopyridine nucleotide is progressing through the aerobic cytochrome system and through the anaerobic lactate-pyruvate system. With significant reduction of oxygen concentration, a greater fraction of the total diphosphopyridine nucleotide oxidation is accomplished by pyruvate, causing an increase in blood lactate and in the blood lactate to pyruvate ratio (L/P ratio). The reaction, pyruvate ⇄ lactate, is catalyzed by the enzyme, lactic dehydrogenase.

Friedemann and Barborka found that, in the blood of normal adults during exercise, there is a rise of both lactate and pyruvate...
concentrations, the lactate concentration rising more rapidly with consequent elevation of the lactate-pyruvate ratio early following the exertion. They demonstrated that changes in the rate of fall of the lactate-pyruvate ratio followed changes in pulse rate and respiratory rate. They concluded that following exercise the lactate-pyruvate ratio was an indicator of the return of adequate tissue oxygenation. Tepperman and Tepperman showed that there was elevation of the blood lactate-pyruvate ratio of normal individuals exercising while breathing air under reduced barometric pressure. The elevation of the lactate-pyruvate ratio observed at a simulated altitude of 5000 feet was suppressed by breathing 100 per cent oxygen at that altitude.

The lactate-pyruvate ratio has not been studied heretofore under the conditions prevailing in children with congenital heart disease.

**Experimental**

Values first were established for the venous blood lactate concentration, pyruvate concentration, and lactate-pyruvate ratio in 42 normal adults and in 16 normal children. The normal children included patients hospitalized but ambulatory and afebrile. These children were usually late convalescents after elective surgical operations. There was no significant difference between the values for the hospitalized children in this group, and the values observed in several well children attending the outpatient clinic as tuberculosis contacts.

The children with congenital heart disease were studied under hospital conditions. The diagnosis of congenital heart disease, cyanotic and acyanotic, was made by the usual clinical and laboratory evidences of heart disease. In most instances the anatomic lesion was confirmed at the time of surgery or autopsy, or by the corollary evidence of improvement of cyanosis following the Blalock-Taussig operation. The acyanotic type of congenital heart disease was represented exclusively by patients with patent ductus arteriosus. The cyanotic group consisted predominantly of children with the tetralogy of Fallot.

**Methods**

Blood samples were drawn from an antecubital vein whenever possible. In some of the younger children it was necessary to use the femoral vein, or rarely, the external jugular vein. During serial sampling for the exercise

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**Figure 1.** Diagrammatic illustration of the alternative pathways for the maintenance of oxidized diphosphopyridine nucleotide (Coenzyme I, DPN): aerobically through the cytochrome-oxidase system, anaerobically through the pyruvate-lactate conversion system.
test, the arm veins were used exclusively. Use of a tourniquet was necessary in order to obtain blood samples rapidly from the children. The tourniquet was kept in place as short a time as possible and, where feasible, released after entry into the vein with a short waiting period prior to withdrawal of the blood. No systematic differences were observed using this tourniquet technic alternately in 15 adults (table 2). Arterial blood samples were drawn from the femoral vessels. Uncalibrated 10 ml. syringes were used for sampling. After ejecting any foam present in an 8–10 ml. sample, a portion of the blood was delivered under oil into an oxalate-fluoride tube. Ejection of blood from the syringe was stopped exactly at the 5.2 ml. mark. Five milliliters of blood were delivered through the needle into 10 ml. of freshly prepared 20% trichloracetic acid. This technic permitted rapid deproteinization immediately interrupting glycolysis. Blood samples were drawn 2–4 hours after the last meal (breakfast or lunch) and analyzed the same day.

The standard exercise test of Courand and Richards⁸ was used. During this test the patient steps up and down from a stool 20 cm. high 30 times in one minute.

Lactate and Pyruvate. The deproteinized blood sample was centrifuged at 2000 r.p.m. for 10 minutes. Lactate concentration was determined on duplicate 3 ml. aliquots of the supernate by the method of Long.⁶ It was found that the blank recommended by Long was not necessary in our application of the method, probably due to the fact that we have used a 10% solution of reagent grade ceric sulfate rather than the 30% solution of 35% pure ceric sulfate employed by Long. Pyruvate concentration was determined on duplicate 1.5 ml. aliquots of the supernate by the method of Friedemann and Haugen.⁷ During these experiments 142 blood samples were analyzed. The maximum difference between duplicate analyses was 2.7 mg. lactate per 100 ml. blood and 0.10 mg. pyruvate per 100 ml. blood. For lactate, the average difference between duplicate determinations was 1.55 mg. (standard deviation 0.572 mg.). The average difference between duplicates for pyruvate was 0.034 mg. (standard deviation 0.032 mg.).

Carbon dioxide and oxygen content were determined on single one milliliter samples of the blood under oil by the method of Van Slyke and Neill.⁸ Oxygen capacity was determined after equilibration of blood with air at room temperature in a tonometer.

Blood lactic dehydrogenase. The lactic dehydrogenase content of erythrocytes was estimated by a quantitative application of the ferricyanide method for the study of dehydrogenase systems.⁹ In a bicarbonate medium, the reduction of ferricyanide by the hydrogen activated through the dehydrogenase system gives rise to equimolar amounts of carbon dioxide. (The use of ferricyanide as a hydrogen acceptor has the advantages of nontoxicity and nonautooxidizability).

The evolution of carbon dioxide was measured in the Barcroft-Warburg manometric apparatus at a temperature of 38 C. with an oscillation rate of 120 cycles per minute. The reaction cell of the flask contained 3 ml. of a solution of the following composition: sodium bicarbonate, 0.05 M; sodium lactate pH 7.4, 0.10 M; sodium cyanide pH 7.4, 0.05 M; diprophosphopyridine nucleotide, 0.0012 M*; lysed erythrocytes, 0.20 ml.

Sodium cyanide was used to fix the pyruvate produced in the reaction by conversion to the pyruvate cyanohydrin. The final pH of this solution was 7.4 at 38 C. in the gas medium of 90% nitrogen 10% carbon dioxide. Blood containing not more than 2 mg. of potassium oxalate per ml. was centrifuged and the packed cells washed three times with an equal volume of 0.9% sodium chloride solution, the last centrifugation being carried out at 2000 r.p.m. for 10 minutes. The cells then were laked in 5 volumes of distilled water. The diprophosphopyridine nucleotide was reported to be 60% pure by spectrophotometric analysis by the manufacturer. The side arm of the flask contained 0.2 ml. of 10 per cent sodium ferricyanide in 0.05 M sodium bicarbonate. A small square of yellow phosphorus was placed in the center well to eliminate traces of oxygen.

* Nutritional Biochemicals, Inc., Cleveland, Ohio
Following gas and temperature equilibration of the reaction manometers, ferricyanide was tipped into the reaction cell and gas evolution measured for 30 minutes at five minute intervals. Rate of evolution of carbon dioxide during this period was expressed as microliters of carbon dioxide (STPD) produced in nitrogen per hour \( (Q_{CO2}^{STPD}) \). Determinations were run in duplicate.

**Lactic Dehydrogenase Index** = \( \frac{Q_{CO2}^{STPD}}{\text{Cell volume}} \) expressing a figure proportional to the dehydrogenase activity of undiluted whole blood.

**Results**

Table 1 lists the concentrations of blood lactate and blood pyruvate and the L-P ratio in 16 normal children at rest. Significant differences for any of these values were not found between the 8 males and 8 females, or between the group of 11 children who did not cry or struggle during the blood sampling and the group of 5 children who cried and/or struggled to a varying degree. Table 2 summarizes similar data obtained in 42 normal adults. There was no significant difference between the 32 adult males and 10 adult females.

The values for lactate concentration, pyruvate concentration, and lactate-pyruvate ratio
were significantly higher in children than in the adults.

<table>
<thead>
<tr>
<th></th>
<th>Lactate mg. per 100 ml. blood</th>
<th>Pyruvate mg. per 100 ml. blood</th>
<th>L-P Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Normal adults</td>
<td>9.36</td>
<td>1.03</td>
<td>9.10</td>
</tr>
<tr>
<td>2. Normal children</td>
<td>14.37</td>
<td>1.22</td>
<td>11.86</td>
</tr>
<tr>
<td>p difference</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The results relating to blood lactate and pyruvate and the L-P ratio obtained in 8 children with acyanotic congenital heart disease are summarized in figure 2.

The differences observed between the normal and acyanotic children were not statistically significant, suggesting normal exercise tolerance in children with patent ductus arteriosus. The cyanotic children showed reduced exercise tolerance clinically, and a significant elevation of lactate-pyruvate ratio immediately and 15 minutes after exercise.

In order to determine the correlation between the L-P ratio and the degree of oxygenation of tissue, the L-P ratio was plotted against approximated mean capillary pO₂. The approximation of mean capillary pO₂ requires several assumptions due to the lack of knowledge concerning the quantitative aspects of oxygen diffusion in the capillaries and lack of knowledge concerning the nature of the oxyhemoglobin dissociation curve of individuals with congenital cyanotic heart disease. A modification of the formula of Barcroft was used.
Table 4.—Lactate, Pyruvate and L-P Ratio in Children with Cyanotic Congenital Heart Disease

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Lactate mg. per 100 ml. blood</th>
<th>Pyruvate mg. per 100 ml. blood</th>
<th>L-P Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. B.</td>
<td>3</td>
<td>M</td>
<td>Tetralogy of Fallot</td>
<td>20.43</td>
<td>1.56</td>
<td>13.10</td>
</tr>
<tr>
<td>C. B.</td>
<td>12</td>
<td>M</td>
<td>Truncus arteriosus; cor triloculare</td>
<td>10.53</td>
<td>0.94</td>
<td>11.20</td>
</tr>
<tr>
<td>T. M.</td>
<td>5</td>
<td>M</td>
<td>Tetralogy of Fallot</td>
<td>14.62</td>
<td>1.36</td>
<td>10.75</td>
</tr>
<tr>
<td>K. C.</td>
<td>1</td>
<td>F</td>
<td>Probable tetralogy of Fallot</td>
<td>41.65</td>
<td>3.41</td>
<td>12.21</td>
</tr>
<tr>
<td>L. K.</td>
<td>4</td>
<td>M</td>
<td>Probable tetralogy of Fallot</td>
<td>15.08</td>
<td>1.38</td>
<td>10.93</td>
</tr>
<tr>
<td>J. S.</td>
<td>6</td>
<td>M</td>
<td>Tetralogy of Fallot and patent ductus arteriosus</td>
<td>10.35</td>
<td>1.04</td>
<td>9.95</td>
</tr>
<tr>
<td>C. L.</td>
<td>4</td>
<td>M</td>
<td>Unknown</td>
<td>13.28</td>
<td>1.29</td>
<td>10.29</td>
</tr>
<tr>
<td>S. S.</td>
<td>5</td>
<td>M</td>
<td>Tetralogy of Fallot</td>
<td>16.54</td>
<td>1.29</td>
<td>12.82</td>
</tr>
<tr>
<td>G. S.</td>
<td>9</td>
<td>M</td>
<td>Unknown</td>
<td>14.69</td>
<td>1.50</td>
<td>9.80</td>
</tr>
<tr>
<td>C. E.</td>
<td>7</td>
<td>M</td>
<td>Tetralogy of Fallot</td>
<td>15.19</td>
<td>1.18</td>
<td>12.87</td>
</tr>
</tbody>
</table>

Average and Standard Deviation (10 children): 17.24 ± 8.65, 1.50 ± 0.68, 11.38 ± 1.20
Average for Normal Children (Table 1): 14.37 ± 2.75, 1.22 ± 0.26, 11.86 ± 1.28
p for Difference: 0.3 > p > 0.2, 0.2 > p > 0.1, 0.4 > p > 0.3

Fig. 2. Response of children to the standard exercise test of Cournand and Richards. Observations were made at rest, immediately prior to exercise, immediately following the exercise, and 15 minutes following the completion of the exercise. ○, mean values of seven normal children; Δ, mean values of six children with patent ductus arteriosus; □, mean values of three children with cyanotic congenital heart disease.

For the approximation of mean capillary oxygen tension in the region drained by the cuneate arm vein:

\[ \text{Mean Capillary pO}_2 = \text{Venous pO}_2 + \frac{(\text{arterial pO}_2 - \text{venous pO}_2)}{3} \]

In the absence of any observations of arterial oxygen saturation or pO$_2$ in the normal and acyanotic groups, an arterial pO$_2$ of 88 mm Hg was assumed. The other pO$_2$ values were determined by plotting from a standard oxyhemoglobin dissociation curve, pH 7.4, using observed oxyhemoglobin saturation values. The assumption must be made that the blood of patients with cyanotic congenital heart disease conforms to the pH 7.4 oxyhemoglobin dissociation curve in the face of a plasma ionic
Fig. 3. Relation of calculated mean capillary pO₂ and lactate-pyruvate ratio as measured by analysis of cubital vein blood. ○, normal children at rest; ●, normal children immediately following Courrède-Richards standard exercise; ○, normal children 15 minutes after completion of standard exercise; ▲, children with patent ductus arteriosus at rest; △, children with patent ductus arteriosus 15 minutes after completion of standard exercise; ■, children with cyanotic congenital heart disease at rest. Regression lines were fitted by the least squares method.

Fig. 4. Relation of lactic dehydrogenase index and hematocrit of venous blood. ○, 9 normal adults and 8 normal children (age range 2 years to 32 years); ▲ child with patent ductus arteriosus; ■, 4 children and 2 adults with congenital cyanotic heart disease. Regression lines were fitted by the least squares method.

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Structure resulting in a normal plasma pH but a significantly lowered plasma pCO₂. This assumption is made on the evidence of Bing's direct measurements of blood oxygen saturation and pO₂. These direct values clump around the pH 7.4 standard oxyhemoglobin dissociation curve.

Figure 3 is a graph of the lactate-pyruvate ratio plotted against mean capillary pO₂ in 34 observations on 29 individuals.

The normal and acyanotic values seem to fit a straight regression line and, by the least squares method, the regression equation, pO₂ = 128 - 6.76 L-P ratio, is derived. However there is a wide range of estimating error about this line as indicated by a standard deviation of established pO₂ points about the line of ±9.78 mm. pO₂. The correlation coefficient is −0.64, which is significantly different from zero (p < 0.01). There appears to be better correlation between pO₂ and L-P ratio in the 6 cyanotic children (r = −0.87, p < 0.05) but the small sample size excludes more extensive statistical analysis.

Blood of the cyanotic children has a higher lactic dehydrogenase enzyme activity by virtue of an increased concentration of red blood cells, there being no significant alteration of the enzyme concentration per unit volume of red cells (fig. 4).

DISCUSSION

The demonstration that the L-P ratio in children with cyanotic congenital heart disease at rest does not differ from that of normal children suggests that oxygen requirements are being met under such conditions. It is evident, however, that the existing balance can be upset easily, as the data from the standard exercise test demonstrate. In normal children and in those with patent ductus arteriosus, the lactate, pyruvate and L-P ratio values, rising following exercise, had returned to levels not significantly different from the resting values 15 minutes following exercise. In the children with cyanotic congenital heart disease, the changes were not only more marked just following exercise but persisted 15 minutes later.

The inverse correlation observed between the L-P ratio and mean capillary pO₂ demon-
strates further the relation of this value to tissue oxygenation. The fact that children with cyanotic congenital heart disease have a normal L-P ratio in spite of a reduced mean capillary pO₂ is good evidence that compensatory mechanisms exist through which such individuals maintain normal oxidative conditions in their tissues at rest.

Recent studies indicate that chronic anoxia does not produce significant elevation of iron-porphyrin compounds other than hemoglobin. Drabkin\(^{10}\) has shown that the rate of appearance of new cytochrome in regenerating rat liver is unchanged under conditions of chronic anoxia. The myoglobin concentration in skeletal muscle of rats\(^{11}\) and dogs\(^{12}\) remains unchanged after prolonged exposure to barometric pressure reduced sufficiently to produce marked polycythemia. Changes in these and other tissue constituents might occur under conditions of chronic anoxia but a simpler explanation can be advanced. It is known that oxygen requirements often are reduced significantly in cyanotic congenital heart disease. Bing\(^{13}\) reports a series of cyanotic patients in whom the basal metabolic rate averaged \(-24\) per cent. The ability of cyanotic individuals to maintain a normal L-P ratio may be related to this observation of a lowered metabolic rate. The difference observed between the L-P ratio in resting normal children and resting normal adults is of interest in this regard. Standard tables for the basal metabolic rate indicate that the value for normal children is \(26\) per cent higher than the value for normal adults in the age groups of this series. The L-P ratio was increased \(29\) per cent in the normal children here as compared with the normal adults, suggesting a possible correlation between basal metabolic rate and the L-P ratio. The existence of a normal L-P ratio in the presence of a presumably reduced basal metabolic rate in the patients of the cyanotic group suggests that, due to the hypoxic conditions, the L-P ratio is elevated relative to the basal metabolic rate. Direct comparisons between L-P ratio and the rate of oxygen consumption in cyanotic children and hypothyroid cyanotic individuals should resolve this aspect of the problem.

Krogh\(^{14}\) calculated the capillary-cell pO₂ difference necessary to produce a diffusion gradient sufficient to maintain the observed oxygen consumption of mammalian muscle at rest and arrived at a range, \(19-49\) mm. Hg. The reduction of mean capillary pO₂ in cyanotic congenital heart disease to a range of \(24.8-45.4\) mm. Hg and in our series a range of \(13-42\) mm. Hg presents the possibility that the rate of oxygen diffusion may limit the rate of its uptake under such conditions of chronic anoxia and lead to a lowered metabolic rate.

In the face of normal lactate and pyruvate concentrations the normal lactic dehydrogenase assay would indicate that, at least within the red blood cell, there is no increase in the rate of pyruvate-lactate conversion. The findings indicate association between erythrocyte metabolism and the lactic dehydrogenase system, (possibly the maintenance of the iron of hemoglobin in the ferrous state\(^{15}\)).

**SUMMARY**

1. Blood lactate and pyruvate concentrations and lactate-pyruvate ratio values are established for normal adults and normal children. The resting values are significantly higher in children than in adults.
2. Children with acyanotic congenital heart disease have a normal lactate-pyruvate ratio at rest. Children with cyanotic congenital heart disease have a normal resting lactate-pyruvate ratio in spite of a lowered mean capillary oxygen tension. The possibility is presented that the normal lactate-pyruvate ratio in these children is related to their low metabolic rate.
3. The lactate-pyruvate ratio varies inversely with calculated mean capillary oxygen tension at rest and after exercise.
4. There is a delayed return of the lactate-pyruvate ratio to normal following exercise in children with cyanotic congenital heart disease.

**ACKNOWLEDGMENTS**

We are indebted to Dr. Edward S. West for advice and to Dr. Carl E. Hopkins for guidance during statistical analysis of the data.

**REFERENCES**

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The Metabolism of Lactate and Pyruvate in Children with Congenital Heart Disease
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Circulation. 1950;2:536-544
doi: 10.1161/01.CIR.2.4.536

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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the World Wide Web at:
http://circ.ahajournals.org/content/2/4/536

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CORRECTION: In the article entitled "The Metabolism of Lactate and Pyruvate in Children with Congenital Heart Disease" by Richard J. Havel and Elton Watkins, Jr. (Circulation 2: 536, 1950) the following footnote should have appeared: "This work was done under the auspices of a Life Insurance Medical Research Student Fellowship Grant to Dr. Havel."

In the article entitled "A-V Conduction in Auricular Flutter" by M. Besoain-Santander, A. Pick, and R. Langendorf (Circulation 2: 604, 1950), it was not clearly stated that Dr. M. Besoain-Santander was a Fellow of the Division of International Health of the U. S. Public Health Service.