LACTIC ACIDOSIS AND RENAL FUNCTION IN SHEEP

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Acidosis following grain engorgement in ruminants has been attributed to D-lactic acid accumulation (Dunlop and Hammond, 1965). The D-isomer of lactic acid has been reported to be poorly metabolized by ruminant tissue (Hinkson, Hoover and Poulton, 1967; Huber, 1969). Since the rate of D-lactic acid absorption exceeds metabolism, rapid disposal becomes dependent upon renal excretion.

Engorged animals often exhibit symptoms which resemble the syndrome of shock. Traditionally the degree of shock has been judged by the level of systemic arterial pressure. Juhasz and Szegedi (1968) observed a decrease in arterial pressure in glucose engorged sheep, and Dunlop and Hammond (1965) reported a dramatic decline in arterial pressure in a steer in which lactic acid was introduced into the rumen. Severe reductions in arterial pressure should decrease tissue perfusion pressure with subsequent reductions in renal clearance of plasma lactic acid.

The purpose of this study was to investigate the effect of lactic acidosis on renal blood flow and glomerular filtration rate in sheep.

Materials and Methods

Lactic acidosis was produced by the intravenous infusion of lactic acid in six mature ewes ranging in weight from 43.2 to 54.5 kilograms. Renal blood flow and glomerular filtration rate were measured with para-amino hippuric acid (PAH) and inulin, respectively. Renal blood flow was measured in three ewes, glomerular filtration rate was measured in two ewes, and both measurements were conducted simultaneously in one ewe. Following bilateral jugular catheterization, the bladders were catheterized with a size 16 Foley catheter and all animals were hydrated with 1 L. of physiological saline administered intravenously over a period of 1 hour.

Upon completion of hydration, priming solutions of PAH (7 mg./kg.) and/or inulin (26.4 mg./kg.) were administered. The priming solutions were followed immediately by the constant infusion of PAH (0.35 mg./kg./min.) and/or inulin (0.37 mg./kg./min.). An equilibration period of 1-hr. was allowed before measurements were made. Urine was collected at 10-min. intervals during each collection period for the remainder of the experiment, with blood samples obtained at the mid-point of each urine collection period. After the 1-hr. equilibration period, the collection periods consisted of a 40-min. control period, a period of lactic acid infusion, and a 1-hr. post-infusion period. Racemic lactic acid (65% L and 35% D) was infused at the rate of 1.5 gm./min. until the appearance of severe signs of acidosis as evidenced by panting and accelerated respiration and a decreased blood pH. Whole blood pH was determined within 30 sec. of removal with a Dow Corning Model 12 pH meter equipped with a semi-micro combination electrode. Urine and blood PAH and inulin were measured by the procedures of Smith et al. (1945) and Schreiner (1950), respectively. Blood and urine lactic acid were determined by the method of Barker and Summerson (1941). Hematocrit determination was made by the micro-capillary method similar to the procedure described by Natelson (1951).

Renal blood flow and glomerular filtration rate were calculated using the following formulae:

$$C_{PAH} = \frac{U_{PAH} \times V}{P_{PAH}}$$

$$RBF = \frac{C_{PAH}}{1 - \text{hematocrit}}$$

$$C_{I} = \frac{U_{I} \times V}{P_{I}}$$

Where:

- $C_{PAH}$ = Clearance of PAH
- $U_{PAH}$ = Urine PAH concentration
- $V$ = Urine Volume
- $P_{PAH}$ = Plasma PAH concentration
- RBF = Renal blood flow
- $U_{I}$ = Urine inulin concentration
- $P_{I}$ = Plasma inulin concentration
- $C_{I}$ = Clearance of inulin

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2 Department of Physiology and Pharmacology.
Results and Discussion

Table 1 contains the means and standard deviations of renal blood flow and corresponding blood pH and lactic acid concentrations. Statistical procedures consisted of analysis of variance and multiple range test (Duncan, 1955). Reported renal blood flows are not absolute flow rates since plasma protein-bound PAH, which is incompletely filtrable through glomerular capillaries, was not measured. The kidneys receive from 20 to 25% of the cardiac output. Clark (1927) estimated the cardiac output of a 50 kg. sheep to be approximately 3,980 ml./min. Calculations using these data would suggest that approximately 17 percent of the plasma PAH was protein-bound. Thus, absolute flow rates would appear to be 17% greater than the observed flow rates.

Significant differences (P<.01) were obtained between control renal blood flows and flow rates at 0, 10, 20 and 30 min. and differences were significant at the 5% level at 40 and 50 minutes. Significant (P<.05) reductions in blood pH were observed at 0, 10 and 30 minutes. The large standard deviation observed at 20 min. is undoubtedly responsible for the absence at this time period of a significant reduction. Zero-time represents the last 10 min. of the lactic acid infusion period. Previous investigations have shown that metabolic acidosis significantly reduces systemic arterial blood pressure. Simmons and Olver (1965) have observed in the dog a progressive fall in arterial pressure with decreases in pH. A reduction of 0.6 in blood pH was associated with a 40% reduction in renal blood flow. In the present studies a reduction in blood pH of 0.55 (0-time) resulted in a 40.6% decrease in renal blood flow. In sheep experimentally engorged with glucose, Juhász and Szegedi (1968) reported a reduction in carotid pressure from 110 mm. to 95 mm. Hg. when blood pH was 7.31 and a blood lactic acid concentration of 15 mM/L. An increase in blood lactic acid concentration to 18.6 mM/L. reduced the blood pH to 7.11. At these conditions the carotid pressure fluctuated between 20 and 60 mm. Hg. Since similar blood lactic acid concentration (17.7 mM/L. or greater) and blood pH (7.30 or lower) in the present study were associated with significant reductions in renal blood flow, it would appear that the reduced flows were the result of reduced systemic pressure. In an attempt to delineate the relationship of acidosis and reduced systemic pressure, Wildenthal et al. (1968) infused lactic acid into dogs under conditions which allowed for constant heart rate, aortic pressure and flow. Significant depressions in ventricular contractility were apparent at pH 7.1 and 6.8. These reductions in blood pH were similar to pH decreases associated with reduced renal blood flows in the present work.

Table 2 contains the means and standard deviations of glomerular filtration rate, blood lactic acid concentrations and blood pH. Glomerular filtration rates were decreased over the entire period but only the 0 and 10 min. rates were significantly (P<.05) lower than the control values. Blood pH was significantly (P<.05) reduced at 0, 20, 30, 40 and 50 minutes. The magnitude of reductions in glomerular filtration rates were not proportional to those observed in renal blood flow. In mild hypotension glomerular filtration may not be altered significantly because of simultaneous constriction of the efferent glomerular arterioles and, thus, the

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### Table 1. Renal Blood Flow, Blood Lactic Acid and Blood pH Following Lactic Acid Infusion

<table>
<thead>
<tr>
<th>Period</th>
<th>Renal Blood Flow ml./min.</th>
<th>Blood Lactic Acid mM./L.</th>
<th>Blood pH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D. *</td>
<td>Mean</td>
</tr>
<tr>
<td>Control</td>
<td>681.7</td>
<td>14.9</td>
<td>1.0</td>
</tr>
<tr>
<td>0</td>
<td>318.9**</td>
<td>123.2</td>
<td>33.7</td>
</tr>
<tr>
<td>10</td>
<td>302.2**</td>
<td>113.8</td>
<td>28.5</td>
</tr>
<tr>
<td>20</td>
<td>450.2**</td>
<td>95.5</td>
<td>31.5</td>
</tr>
<tr>
<td>30</td>
<td>501.9**</td>
<td>116.3</td>
<td>27.8</td>
</tr>
<tr>
<td>40</td>
<td>534.4*</td>
<td>162.3</td>
<td>21.5</td>
</tr>
<tr>
<td>50</td>
<td>562.4*</td>
<td>65.5</td>
<td>17.7</td>
</tr>
<tr>
<td>60</td>
<td>644.4</td>
<td>56.9</td>
<td>16.4</td>
</tr>
</tbody>
</table>

** Significantly (P<.01) different from control.
* Significantly (P<.05) different from control.

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*a Standard deviation.
TABLE 2. GLOMERULAR FILTRATION RATE (GFR), BLOOD LACTIC ACID AND BLOOD pH FOLLOWING LACTIC ACID INFUSION

<table>
<thead>
<tr>
<th>Period</th>
<th>GFR ml./min. Mean</th>
<th>S.D.*</th>
<th>Blood Lactic Acid mM./L. Mean</th>
<th>S.D.*</th>
<th>Blood pH Mean</th>
<th>S.D.*</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>88.3</td>
<td>5.9</td>
<td>1.0</td>
<td>0.22</td>
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<td>0</td>
<td>38.8*</td>
<td>10.5</td>
<td>34.2</td>
<td>4.40</td>
<td>6.72*</td>
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<td>10</td>
<td>46.8*</td>
<td>7.6</td>
<td>30.6</td>
<td>0.82</td>
<td>6.89</td>
<td>0.30</td>
</tr>
<tr>
<td>20</td>
<td>61.6</td>
<td>12.8</td>
<td>24.9</td>
<td>0.09</td>
<td>7.14*</td>
<td>0.05</td>
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<tr>
<td>30</td>
<td>78.9</td>
<td>9.2</td>
<td>20.9</td>
<td>1.30</td>
<td>7.19*</td>
<td>0.03</td>
</tr>
<tr>
<td>40</td>
<td>80.5</td>
<td>10.3</td>
<td>17.1</td>
<td>2.60</td>
<td>7.23*</td>
<td>0.04</td>
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<td>50</td>
<td>79.7</td>
<td>10.1</td>
<td>15.8</td>
<td>2.10</td>
<td>7.25*</td>
<td>0.03</td>
</tr>
<tr>
<td>60</td>
<td>81.5</td>
<td>5.5</td>
<td>13.6</td>
<td>2.30</td>
<td>7.33</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Significantly (P<.05) different from control.

Significantly different from control.

The transport maximum for lactic acid reabsorption from the tubules was calculated. This calculation was made during the 60-minute collection period at which time neither the renal blood flow nor the glomerular filtration rate differed from control values. The quantity filtered per minute minus the quantity excreted per minute equals the quantity reabsorbed per minute. Such calculations yielded a value of 66.4 mg. per minute.

Summary

The effect of lactic acidosis on renal blood flow and glomerular filtration rate was studied in sheep. Renal blood flow was significantly reduced with blood lactic acid concentrations of 17.7 mM./L. or greater and a blood pH of 7.30 or less. The magnitude of reduction in glomerular filtration rate was not proportional to those observed in renal blood flow. Significant reductions in glomerular filtration rate were observed with blood lactic acid concentrations of 30.6 mM./L. or greater and a blood pH of 6.89 or lower. Tubular reabsorptive transport maximum for lactic acid was calculated to be 66.4 mg. per minute.

Literature Cited


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Huber, T. L. 1969. Effect of ration on liver oxidation...