INSULIN-SECRETING CAPACITY IN NEWBORN INFANTS

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The normal adult and older children exhibit an immediate insulin secretory response with peak insulin levels being reached within 5–10 minutes after a rapid intravenous glucose injection. It has been shown that the newborn disposes of glucose slowly,1,2 and that plasma insulin response to intravenous glucose injection is significantly delayed in newborn infants.3–5

Isles et al demonstrated that a very high insulin level is reached in the umbilical vein approximately 60 minutes following a rapid intravenous glucose injection and that there is a rapid change in plasma insulin values from one specimen to the next during the intravenous glucose tolerance test in normal newborn infants.6 Their findings may provide a basis for the divergent interpretation of insulin secreting capacity of the normal newborn infants without the knowledge of the neonatal vascular anatomy. In newborn infants the umbilical vein has been used as a source of blood sampling, as it is readily available for repeated blood sampling.

The umbilical vein receives blood supply from the portal vein directly proximal to the pancreatic vein.

It is obvious that the previous data based on the umbilical vein blood await reevaluation in order to assess the effect of blood glucose concentration on insulin output in the normal newborn infant.

The present study is an attempt to test more directly the view that a diminished secretory capacity of the pancreas is a characteristic feature of normal newborn infants, by determining the plasma insulin response to intravenously administered glucose in specimens obtained from both the umbilical artery and umbilical vein.
MATERIALS AND METHODS

Intravenous glucose tolerance tests were performed on 8 normal newborn infants within 3-6 hours after birth. All infants were born by vaginal delivery to apparently normal mothers. Maternal diabetes mellitus was carefully excluded by family history and multiple urinalyses on each mother. Each infant weighed between 2800 and 3800 g. All feedings were withheld prior to the tolerance test. The clinical details are shown in Table 1. Glucose tolerance was measured in all infants by the technique of rapid intravenous injection of glucose. Twenty percent glucose solution was infused over 2-3 minutes to a total dose of 0.5 gram per kilogram of body weight. Blood samples were obtained for sugar and insulin at 10 minutes intervals prior to and after the glucose injection, via polyvinyl catheters inserted into the umbilical vein and artery. The umbilical vein catheter was inserted to a distance of approximately 8 cm from the abdominal wall and maintained throughout the course of the test. An radiologic confirmation of the location of the catheter tip was made in some but not all infants. Since the catheter was inserted into the umbilical vein, it is tentatively described as the umbilical vein catheter in this paper. During the study the infants were in a warm room (86°F) and the umbilical vein and artery were catheterized under aseptic technique. Each volume removed for sampling was immediately replaced with the same amount of normal saline.

Plasma insulin levels were determined by the double antibody immunoassay method of Hales and Randle.7 Blood sugar concentrations were analyzed by the Somogi-Nelson method.8

<table>
<thead>
<tr>
<th>Age of mother (Yr.)</th>
<th>Parity of mother</th>
<th>Maturity of baby (Wk.)</th>
<th>Weight of baby</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>1</td>
<td>42</td>
<td>3030</td>
</tr>
<tr>
<td>25</td>
<td>1</td>
<td>39</td>
<td>2555</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>40</td>
<td>3800</td>
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<td>0</td>
<td>41</td>
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</tr>
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<td>29</td>
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<td>40</td>
<td>3080</td>
</tr>
<tr>
<td>36</td>
<td>2</td>
<td>39</td>
<td>2800</td>
</tr>
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<td>0</td>
<td>41</td>
<td>3730</td>
</tr>
<tr>
<td>24</td>
<td>1</td>
<td>42</td>
<td>3240</td>
</tr>
</tbody>
</table>
RESULTS

Blood samples were obtained simultaneously through the catheters in the umbilical vein and artery. Levels of insulin in plasma were determined during intravenous glucose tolerance test starting at 3-6 hours of age.

Table 2

<table>
<thead>
<tr>
<th>Time after glucose injection (minutes)</th>
<th>No. of infants</th>
<th>Sugar (mg/dl)</th>
<th>Mean</th>
<th>S.D.</th>
<th>Insulin (μU/ml)</th>
<th>Umbilical artery</th>
<th>Mean</th>
<th>S.D.</th>
<th>Umbilical vein</th>
<th>Mean</th>
<th>S.D.</th>
<th>P. Umbilical vein vs. artery vs. vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>8</td>
<td>59.9</td>
<td>11.1</td>
<td></td>
<td>21.4</td>
<td>11.8</td>
<td>39.5</td>
<td>36.4</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>190.0</td>
<td>38.3</td>
<td></td>
<td>20.2</td>
<td>10.1</td>
<td>50.4</td>
<td>27.9</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>6</td>
<td>160.9</td>
<td>23.3</td>
<td></td>
<td>20.4</td>
<td>10.7</td>
<td>73.0</td>
<td>39.7</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>30</td>
<td>8</td>
<td>149.8</td>
<td>22.5</td>
<td></td>
<td>44.1</td>
<td>30.2</td>
<td>140.5</td>
<td>45.7</td>
<td>0.01</td>
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<tr>
<td>40</td>
<td>6</td>
<td>136.1</td>
<td>26.4</td>
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<td>76.0</td>
<td>23.6</td>
<td>303.8</td>
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<td>0.01</td>
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<tr>
<td>50</td>
<td>6</td>
<td>118.8</td>
<td>24.4</td>
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<td>34.9</td>
<td>298.2</td>
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<tr>
<td>60</td>
<td>8</td>
<td>106.6</td>
<td>27.1</td>
<td></td>
<td>56.2</td>
<td>26.2</td>
<td>226.4</td>
<td>157.5</td>
<td>0.03</td>
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</tbody>
</table>

Fig. 1 and Table 2 show plasma insulin levels after intravenous glucose injection. Throughout the first hour after the dose of glucose, plasma insulin values were significantly higher in the umbilical vein. At 30-60 minutes follow-
ing intravenous glucose injection when maximal plasma insulin levels were reached in the umbilical vein, the difference of the insulin values is most prominent between the umbilical vein and artery. The striking feature is that there is a sharp swing in the insulin concentrations of the umbilical vein, while plasma insulin levels remain relatively constant in the umbilical artery. A marked difference in plasma insulin values is evident between the umbilical vein and artery. Glucose removal from the plasma is definitely delayed as previously reported by others.1,2

DISCUSSION

Our study clearly demonstrates that there is a marked difference in plasma insulin concentrations between the umbilical vein and artery during an intravenous glucose tolerance test. These data are essentially in accordance with those of Kanazawa et al9 demonstrating a significant difference in plasma insulin levels between pancreatic and femoral veins in dogs.

Pildes et al recently showed that there is a significant difference of plasma insulin concentration in the peripheral and umbilical vein during oral glucose tolerance test in the newborn infants of gestational diabetic mothers.10

In the evaluation of our present data, knowledge of the anatomy of the neonatal vascular circulation is essential. The umbilical vein catheter may transverse the ductus venosus and then enter the inferior vena cava. It may enter portal sinus and portal vein where venous drainage comes directly from the pancreas.11 The exact location of the umbilical catheter was not confirmed radiographically in all infants, but higher plasma insulin levels in the umbilical vein probably reflect aspiration of pancreatic effluent blood from the catheter.

The difference in plasma insulin concentrations between the umbilical vein and artery is most likely explained by hepatic clearing of insulin and dilution of the pancreatic vein blood in systemic circulation. If the umbilical vein catheter is in the inferior vena cava or in the heart, it is expected that there is no significant difference of plasma insulin concentrations between simultaneously obtained samples of the umbilical vein and artery. The site of blood sampling appears critical in the interpretation of an intravenous glucose tolerance test in the newborn infants.

In the light of the present data and the unique neonatal anatomy, it is apparent that normal newborn infants produce relatively small rise in plasma insulin levels in response to hyperglycemia.

A slow insulin response after glucose injection in the umbilical vein (Fig. 1)
definitely confirms the belief that there is normally delayed release of insulin from the stimulated newborn pancreas.

These results now make it clear that this delayed release of insulin in response to intravenous glucose is clearly delayed pancreatic secretion rather than delayed appearance of insulin in the systemic circulation due to other factors.

The finding that the normal newborn infant has a diabetic pattern of pancreatic insulin release seems noteworthy, in connection with the frequency of a decreased insulin response to glucose infusion in the general population.

Luft has proposed that a delayed and low insulin response to hyperglycemia was the common feature of all different stages of diabetes mellitus, from prediabetes, through latent diabetes, to the overt stage of the disease. He found a considerable number of healthy adults with decreased and delayed insulin response to glucose infusion. When the glucose infusion test was performed on 85 unselected healthy adults with normal glucose tolerance, the majority showed the expected prompt and marked increase in plasma insulin. However, 15 to 20 percent of the group the insulin response was similar to that found in diabetic and prediabetic subjects.

It might indicate that a delayed and decreased insulin release is a form of functional immaturity rather than specific for diabetes. In other words, it seems logical to speculate that a diminished response of pancreatic insulin output during the early period of life is maintained throughout life by a diabetic patient. The mechanism of a delayed insulin secretion in newborn infants deserves further investigation.

SUMMARY

Response of plasma insulin to intravenous glucose injection in the umbilical vein and artery were studied in normal newborn infants. Normal newborn infants produce a small rise in circulating insulin levels in response to hyperglycemia despite a delayed excessive insulin levels in the umbilical vein. The relatively poor response of the neonatal pancreatic beta cells to glucose was confirmed.

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REFERENCES