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Postheparin Plasma Lipoprotein and Hepatic Lipases in Preterm Neonates

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ABSTRACT. Postheparin plasma lipoprotein lipase and hepatic lipase activities of 11 preterm infants aged 1 to 4 days were measured 15 min after a heparin bolus of 100 IU/kg and during an exchange transfusion performed with fresh heparinized blood. Each infant had a birth weight (range, 1210–3490 g) appropriate for gestational age (range, 28–36 (wk). Eight of the infants (group 1) were in good clinical condition while three (group 2) suffered from septic shock. After the heparin bolus and during the exchange transfusion, lipoprotein and hepatic lipase activities in group 1 were higher than in term infants. In group 2, both lipase activities were extremely low after the heparin bolus but increased approaching the activities of group 1 during the exchange transfusion. Clearance of fat from the circulation is slower in preterm than term infants. This has been attributed to low lipoprotein lipase activity. Our results, however, indicate that lipoprotein lipase is not the reason for slow clearance of fat from the circulation in preterm infants except in septic shock. (*Pediatr Res* 18:1104–1107, 1984)

Abbreviation

FFA, free fatty acids

Postheparin plasma lipolytic activity has been used as a measure of lipoprotein lipase activity in newborns (3, 7, 20). In very low birth weight infants, postheparin plasma lipolytic activity is low (3, 20), and fat tolerance tests suggest a slow disposal of lipids infused (1, 4, 14, 17). Therefore, it has been assumed that lipoprotein lipase activity is low in preterm infants (1, 3, 17, 20).

However, postheparin plasma lipolytic activity also contains hepatic lipase activity, whose function in triglyceride metabolism has not been established (6, 12, 18). In term infants, hepatic lipase activity is about three times the lipoprotein lipase activity, and the two lipase activities can vary independently (16). Thus, postheparin plasma lipolytic activity seems to be unsuitable for the evaluation of lipoprotein lipase activity.

We now report specific postheparin plasma lipoprotein and hepatic lipase activities of 11 preterm infants, measured in connection with an exchange transfusion performed because of hyperbilirubinemia, blood group incompatibility, or septicemia.

MATERIALS AND METHODS

Patients. We studied 11 infants, four girls and seven boys. Nine mothers were healthy. One mother had hypertension because of glomerulonephritis and was treated with clonidine and dihydralazine during the 3 wk preceding delivery. Another mother had idiopathic thrombocytopenia; she received prednisolone during the whole pregnancy.

Six mothers had premature rupture of membranes between 0.5 and 14 days before delivery. Four infants were delivered by cesarean section, the others through vaginal route.

All infants were preterm and of appropriate weight for gestational age. On the basis of clinical findings we divided the infants into two groups. Group 1 consisted of eight infants who were not severely ill. Group 2 consisted of three infants who suffered from septic shock.

Group 1. The mean gestational age was 33.5 wk (range, 28–36). The mean birth weight was 2244 g (range, 1210–3490). Two infants had Apgar scores less than seven at the age of 1 or 5 min. The infants were fed with breast milk; five of them received glucose intravenously too. At the time of the exchange transfusion, the postnatal ages ranged from 4 to 43 h.

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The indications for exchange transfusion were hyperbilirubinemia, blood group incompatibility, and suspected septicemia. Three infants had hyperbilirubinemia due to blood group incompatibility: two had anti-B and one anti-D immunization. In addition, one infant had simple hyperbilirubinemia and another anti-D immunization with low hemoglobin and high reticulocytes. Three other infants were suspected to have septicemia, which later proved to be respiratory distress syndrome without infection; all recovered completely. During the exchange transfusion, these three infants were mechanically ventilated.

The mean blood glucose was 86.4 mg/dl (range, 14.4–234); two infants were hyperglycemic and one was hypoglycemic. The mean serum insulin was 34.6 microunits/ml (range, 5.3–130.7). The mean serum cholesterol and triglyceride concentrations were 69.7 (range, 34.1–98.5) and 58.1 mg/dl (range, 31.7–141). The mean apolipoprotein A-I and A-II concentrations were 82.3 (range, 53.0–119) and 24.8 mg/dl (range, 17.7–36.1).

Group 2. The gestational ages of three septic preterm infants were 29, 31, and 33 weeks. Their birth weights were 1420, 1480, and 2190 g; the Apgar scores were six, seven, and nine at the age of 1 min. The infants were fed with glucose given intravenously but they also received some breast milk. At the time of the exchange transfusion, the postnatal ages were 23, 29, and 98 h.

The reason for exchange transfusion was septic shock; all three infants had granulocytopenia, poor peripheral circulation with arterial hypotension, low transcutaneous oxygen pressure, and respiratory distress that required mechanical ventilation. In two of the infants, the causative organism was β-hemolytic *Streptococcus* group B; one infant died of massive intraventricular hemorrhage 6 days after the exchange transfusion, and the other died of pulmonary complications at the age of 2 months. In the third infant, *Escherichia coli* was cultured from the umbilical catheter. The infant had also a small subependymal hemorrhage but recovered completely.

The blood glucose concentrations of three septic preterm infants were 41.4, 72.0, and 119 mg/dl. Their serum insulin values were 18.6, 27.7, and 51.5 microunits/ml. Their serum cholesterol concentrations were 38.7, 58.1, and 105 mg/dl and their serum triglyceride concentrations were 28.2, 36.1, and 44.4 mg/dl. Their apolipoprotein A-I concentrations were 55.9, 81.2, and 81.3 mg/dl and apolipoprotein A-II concentrations were 19.5, 26.6, and 32.0 mg/dl.

Study protocol. All 11 infants underwent one exchange transfusion performed routinely with fresh heparinized blood from voluntary donors. Blood was exchanged through an umbilical catheter. Before the exchange, a blood sample was taken through the catheter to determine serum triglyceride, cholesterol, insulin, apolipoproteins A-I and A-II, and blood glucose concentrations, and plasma lipoprotein lipase and hepatic lipase activities. Thereafter, a heparin bolus of 100 IU/kg was injected through the catheter and a blood sample was taken 15 min later to measure the lipase activities. The conventional exchange transfusion (200 ml/kg) was then performed; removal of 5 to 10 ml of infant blood alternated with replacement of 5 to 10 ml of fresh heparinized (4.5 IU/ml) donor blood that contained no measurable lipase activities. When 100 and 200 ml/kg of blood had been exchanged, blood samples were taken to measure again lipoprotein and hepatic lipase activities. Heart rate, respiration, transcutaneous oxygen tension, blood pressure, and central venous pressure were monitored. All infants tolerated the exchange without complications.

Biochemical assays. Blood glucose and serum insulin were determined by routine laboratory methods. Cholesterol and triglyceride concentrations in serum were measured with an enzymatic method (commercial reagent kit No. 187313 for cholesterol and No. 297771 for triglycerides; Boehringer Diagnostica GmbH Mannheim, West Germany). Apolipoprotein A-I and A-II concentrations were measured with a radial immunodiffusion method (2). Lipoprotein lipase and hepatic lipase activities were measured in postheparin plasma by the method of Huttunen *et al.* (6). In this method lipoprotein lipase activity is determined in the presence of hepatic lipase antiserum prepared in rabbits against purified human postheparin plasma hepatic lipase. For measuring hepatic lipase activity, lipoprotein lipase is inhibited by 1 M NaCl and by omission of serum activator. The substrate is a labeled triolein emulsion prepared by sonication. Each assay series included two standard samples of human postheparin plasma for correction of variations in substrate emulsification.

Statistical methods. Statistical analyses were performed using the Mann-Whitney and Wilcoxon two-tail tests of the BMDP statistical software.

The Ethical Committee of the Children's Hospital, University of Helsinki, had approved of the study.

RESULTS

Postheparin Plasma Lipase Activities. Group 1. The blood samples taken before heparin administration contained no measurable lipase activities. Fifteen min after the heparin bolus of 100 IU/kg, the mean activities were 26.8 μmol FFA/ml/h (SEM 4.7) for lipoprotein lipase (Fig. 1*A*) and 64.1 μmol FFA/ml/h

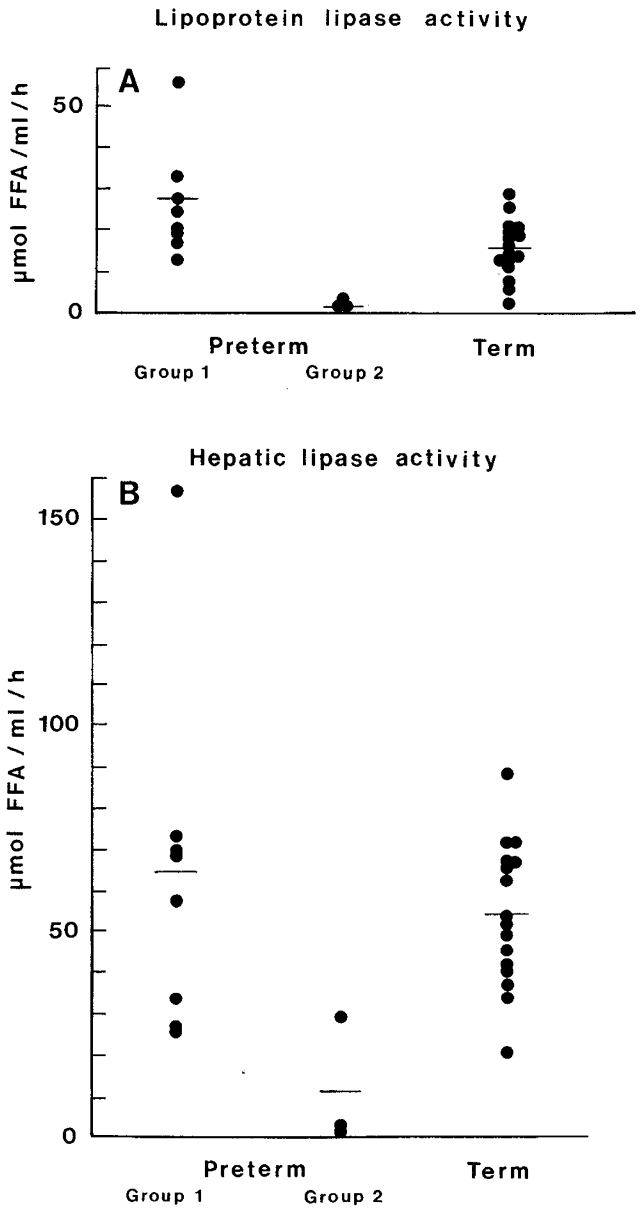

Fig. 1. Postheparin plasma lipase activities in preterm infants. Activities of lipoprotein lipase (*A*) and hepatic lipase (*B*) were measured in eight preterm infants (group 1) and in three preterm infants with septic shock (group 2); the activities in 16 term infants are shown for comparison (16). The mean activities are indicated by *short horizontal lines.*

(SEM 15.0) for hepatic lipase (Fig. 1*B*). The mean lipoprotein lipase activity is higher ($p = 0.025$) than that of term infants (16) but the mean hepatic lipase activity is similar ($p = 0.76$) to that of term infants.

Group 2. In the two infants with streptococcal septicemia, the blood samples taken before the heparin bolus contained no measurable lipase activities, whereas in the third infant with *Escherichia coli* sepsis, low but measurable lipoprotein and hepatic lipase activities were found already before heparin administration. Fifteen min after the heparin bolus of 100 IU/kg, the mean activities were 1.75 μmol FFA/ml/h (SEM 1.3) for lipoprotein lipase (Fig. 1*A*) and 11.2 μmol FFA/ml/h (SEM 9.2) for hepatic lipase (Fig. 1*B*). The means of lipoprotein ($p = 0.014$) and hepatic ($p = 0.041$) lipase activities were lower that those of group 1.

Lipase Activities during the Exchange Transfusion. The exchange started 15 min after the heparin bolus. Blood samples were taken, on the average, 43 and 78 min after the bolus, when 100 and 200 ml/kg of blood had been exchanged.

Group 1. Lipoprotein lipase activity (Fig. 2*A*) remained almost unchanged ($p > 0.35$) during exchange transfusion. In contrast, the mean hepatic lipase activity (Fig. 2*B*) decreased ($p = 0.018$) during exchange transfusion. Thus, when 100 and 200 ml/kg of blood had been exchanged, the mean hepatic lipase activities were 39 and 22% of the activity found at 15 min after the heparin bolus. Hence, both lipase activities behaved as in term infants (16) during exchange transfusion.

Group 2. In contrast to group 1, the mean lipoprotein (Fig. 2*A*) and hepatic (Fig. 2*B*) lipase activities of group 2 first increased and then decreased during the exchange transfusion.

DISCUSSION

In preterm infants, lipoprotein lipase activity has not been previously measured with specific methods but on the basis of postheparin lipolytic activity (3) and fat tolerance tests (1, 4, 14, 17), it is generally assumed that lipoprotein lipase activity is low in preterm infants. However, when measured with specific methods, lipoprotein lipase activity in preterm infants (group 1) older than 28 gestational weeks and over 1200 g in weight was found to be higher than in term infants and adults. The result indicates the lipoprotein lipase activity is not the reason for slow clearance of fat from the circulation in preterm infants. Instead, slow clearance results probably from other factors such as smaller mass of adipose tissue or immaturity of liver (1, 14, 17).

Insulin concentration (34.6 microunits/ml) in preterm infants is considerable higher than in term infants (16). This may explain the difference in lipase activity between preterm and term infants, because insulin is a known activator of lipoprotein lipase (13).

In infants (group 1 in Fig. 1*A*) and adults (16), interindividual variability of lipoprotein lipase activity is large. Hence, there are infants and adults whose lipoprotein lipase activity is low. Their fat clearance is probably slower than the average, because lipoprotein lipase activity is the rate-limiting factor for clearance of fat from the circulation (13).

As in term infants, hepatic lipase activity in preterm infants was 2–3 times the activity of lipoprotein lipase. The importance of high hepatic lipase activity in infants cannot be evaluated at present because the function of hepatic lipase has not been established (5, 8, 11).

The three infants with septic shock (group 2) had extremely low lipase activities when measured 15 min after the heparin bolus of 100 IU/kg. During the exchange transfusion, their lipase activities, however, increased approaching the activities in group 1. A few hours before the exchange transfusion, all three infants had received red blood cells, granulocytes, or fresh frozen plasma which all contain heparin. This is not a probable reason for the lack of increase in lipoprotein lipase activity after the heparin bolus because studies on postheparin plasma lipolytic activity suggest that even a continuous heparin infusion does not deplete lipoprotein lipase activity in very low birth weight infants (20).

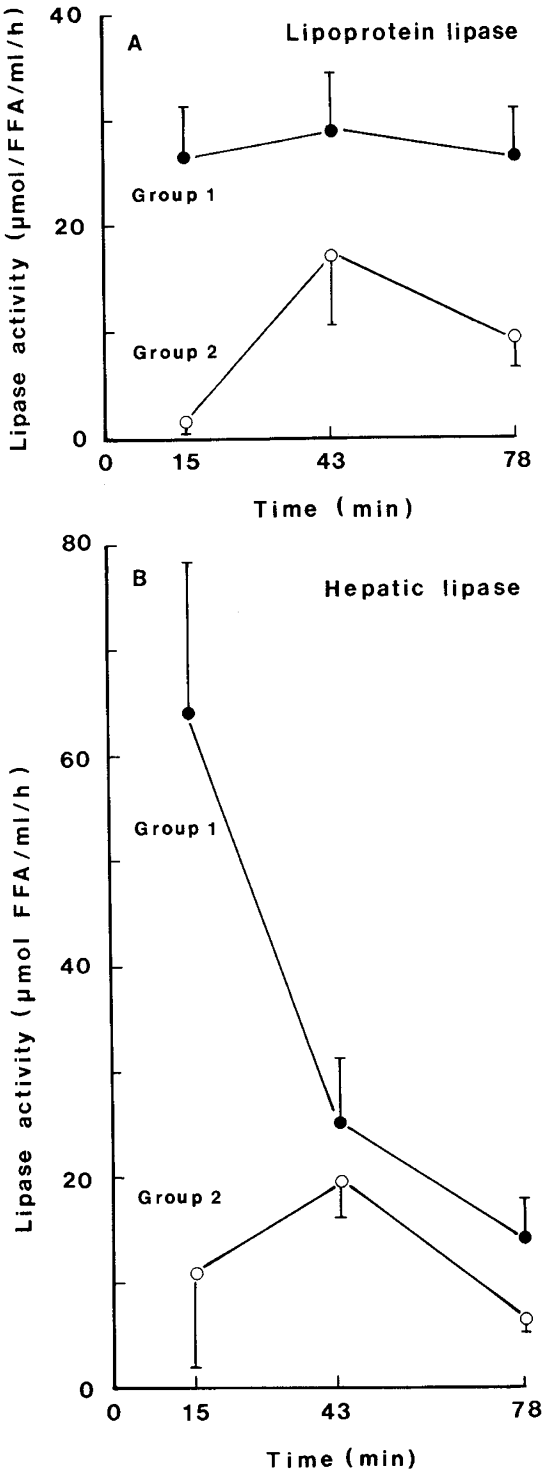

Fig. 2. Lipase activities in eight preterm (group 1) and three septic preterm infants (group 2) during the exchange transfusion (mean ± SEM).

On the other hand, there is evidence that endotoxin degrades vascular endothelium (15), which may account for the decrease of the endothelial lipase activities. In addition, endotoxin may suppress lipoprotein lipase activity (9, 10). These two observations provide an explanation for the finding that the increase of lipase activities after the heparin bolus was very small or absent. During the exchange transfusion, heparin concentration increases (16), releasing lipase activities from a nonendothelial pool (13), and endotoxin concentration decreases (19), which may explain the increase of lipase activities towards those found in group 1. Thus, our preliminary observations suggest that in

infants with endotoxin shock the clearance of fat from the circulation may be defective and, therefore, fat should be administered with care.

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Carbohydrate Tolerance in Cystic Fibrosis Is Closely Linked to Pancreatic Exocrine Function

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ABSTRACT. We evaluated carbohydrate tolerance in nine thin cystic fibrosis (CF) patients and in six controls, measuring responsiveness to the following insulinotropic secretagogues: oral glucose, IV glucose, and IV tolbutamide. Glucose responses segregated patients into two groups: Group I with normal carbohydrate tolerance associated with normal to slightly increased insulin responses, and Group II with impaired carbohydrate tolerance associated with insulinopenia. This latter group included one patient with frank diabetes. The CF patients demonstrated a significant positive correlation between insulin secretion, in response to each secretagogue, and pancreatic exocrine function as measured by serum pancreatic amylase isoenzyme concentration. Pancreatic α-cell function, as reflected by basal plasma glucagon concentrations, also correlated well with exocrine function in the CF patients, excluding the diabetic individual. The enteroinsular axis of the CF group was intact as reflected by normal plasma gastric inhibitory polypeptide concentrations in Group I and by elevated levels, basally and in response to oral glucose, in the insulinopenic Group II patients. Furthermore, those patients with impaired tolerance demonstrated a greater magnitude of insulinopenia compared to controls following IV glucose and possibly IV tolbutamide, than following oral glucose.

Thus, these data suggest that loss of carbohydrate tolerance in patients with CF, like that seen with classical chronic pancreatitis, 1) parallels the loss of exocrine function, 2) is associated with appropriate enteroinsular sig-

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