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Glomerular filtration rate in the preterm infant: the relation to gestational and postnatal age

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Abstract. In 41 preterm neonates with a gestational age (GA) varying from 27 to 36 weeks, glomerular filtration rate (GFR) was measured by means of the continuous inulin infusion technique. The reliability of the technique was confirmed. During postnatal development GFR was found to increase in two ways: firstly, an increase with advancing gestational age, associated with the increase in body weight (BW) [GFR (ml/min) $= 0.15 \times GA - 3.20$, $r = 0.48$, $P = 0.0048$]; secondly, a postnatal increase, being independent from increment in BW. An increase in GFR (ml/min · kg) from 0.88 ± 0.23 to 1.18 ± 0.28 was observed between day 4 and day 11 postnatally ($P < 0.008$). This latter increase is probably associated with changes in renal haemodynamics. No significant influence of artificial ventilation on GFR could be demonstrated in preterm neonates.

Key words: Preterm neonate – Glomerular filtration rate – Development

Introduction

Developmental changes in glomerular filtration (GFR) in neonates and especially in preterm neonates have been the subject of many studies. Increase in GFR with gestational age (GA) has been described by most authors [1, 4, 9, 14], although Aperia et al. [3] reported no increase. Furthermore, data have been published indicating a rapid postnatal increase in GFR [2, 14] contradicted in other studies [9, 20].

The aim of the present study was to establish the effect of GA on the development of GFR together with that of postnatal age (PA). As the role of artificial ventilation on renal function is not completely defined, the effect of this on GFR was also studied. For these purposes, GFR was measured in 41 preterm neonates using the continuous inulin infusion technique, which has been reported to be a reliable technique, also in the very young infant [10].

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Abbreviations: GFR = glomerular filtration rate; BW = body weight; GA = gestational age; PA = postnatal age; C_{in} = inulin clearance; $t_{½}$ = plasma half life; RDS = respiratory distress syndrome; PDA = persistent ductus arteriosus; PROM = premature rupture of membranes

Patients and methods

The GFR was measured in 41 preterm neonates, all admitted to the neonatal intensive care unit of the Sophia Children's Hospital. The GA varied between 27 and 36 weeks (mean 30.6 weeks), the PA varied between 3 and 11 days. In 8 infants initial measurements at day 4 or 5 were repeated at day 11 to determine the postnatal increase in GFR. The GA was estimated from the mother's menstrual history and on physical assessment using the criteria of Dubowitz et al. [12]. Birth weight varied from 810 to 2735 g (mean 1384 g). All infants were in a stable clinical condition at the time of study. Infants receiving nephrotoxic drugs were not included.

Relevant clinical data are summarized in Table 1. Fifteen neonates needed artificial ventilation.

GFR measurement. Inulin was administered as a glucose-10% inulin solution containing 25 g inulin/l at an infusion rate of 0.6 ml/kg · h. After 24 h of infusion, the inulin clearance (C_{in}) was calculated from the infusion rate (R), the inulin level in the infusate (I) and the plasma inulin level (P) as follows:

$$\left(C_{in} = \frac{I \cdot R}{P}\right).$$

The protocol was only performed when intravenous therapy was obligatory. Blood was drawn, when possible, together with that for other laboratory data. Informed parental consent was obtained.

Inulin determination. At least 75 µl serum was deproteinized with an equal volume of 0.6N $HClO_4$ and centrifuged. The amount of endogenous glucose and fructose in serum was measured immediately (A_1). Serum was incubated for 15 min at 70°C during which time inulin was converted into fructose (A_2). The difference between A_2 and A_1 is the amount of fructose originating from the acid hydrolysis of inulin. The determination of fructose was performed by an enzymatic method (Boehringer Mannheim 716260) adapted to a Cobas Bio Analyser (Hoffman La Roche, Basel) [5]. Serum blank values of fructose-like substances were determined as soon as possible after deproteinization. The recovery of inulin at 200 mg/l and 500 mg/l was determined.

Statistics. All values are expressed as mean ± SD. Differences between the mean values of groups of infants with or without artificial ventilation were tested using the Mann Whitney test. The GFR values measured in the infants at day 4 and 11 were

Table 1. Clinical data of the study group

Patient no.	Gestational age (weeks)	Birth weight (g)	Day of GFR measurement	Diagnosis[b]	Artificial ventilation	GFR (ml/min)
1	30.0	1930	4[a]	RDS	–	2.51
2	30.0	1010	4	RDS, PDA	–	1.14
3	30.4	910	11	–	–	1.06
4	34.0	1940	4	RDS, hyperbilirubinaemia	–	1.80
5	29.0	1580	4[a]	RDS, asfyxia	+	0.77
6	29.0	1380	4	RDS, hyperbilirubinaemia	+	1.41
7	28.0	1250	4	Hyperbilirubinaemia	–	1.63
8	29.0	1240	4	RDS, pneumonia, hyperbilirubinaemia	+	1.44
9	29.4	1330	4[a]	–	–	1.26
10	34.0	1280	4	Pneumonia	–	1.28
11	27.0	970	5[a]	Wet lung disease	+	0.87
12	29.4	1135	11	RDS, PDA	+	0.43
13	34.0	2735	4	RDS, Pneumonia	+	4.67
14	30.0	1210	4[a]	Wet lung disease	–	1.10
15	30.0	1115	4[a]	RDS, PDA	+	1.05
16	30.0	1050	9	–	–	1.10
17	28.0	1010	10	Pneumonia	–	1.13
18	28.4	1100	4	RDS, Pneumonia	+	1.12
19	28.0	1125	10	Pneumonia, asphyxia	+	1.07
20	31.0	1365	11	RDS, pneumonia	+	2.00
21	36.0	2580	4	RDS	+	2.90
22	28.0	1100	4	RDS, PDA, pneumonia	+	1.02
23	31.0	1375	4	–	–	0.99
24	31.0	1920	4	PROM	–	1.98
25	27.0	900	5	RDS, PDA, pneumonia	+	0.68
26	27.0	810	5	RDS, pneumonia	+	0.59
27	34.0	1280	3	Pneumonia	–	1.01
28	32.0	1030	5	–	–	1.09
29	33.0	1140	4	Hyperbilirubinaemia	–	1.05
30	31.0	1670	7	Hyperbilirubinaemia	–	1.26
31	32.0	1930	4[a]	Wet lung disease, hyperbilirubinaemia	–	1.71
32	27.0	1080	7	–	–	1.08
33	33.0	1430	4[a]	Hyperbilirubinaemia	–	1.01
34	33.0	970	4	Pneumonia	–	0.84
35	34.5	2170	4	RDS, wet lung disease	–	2.13
36	30.0	990	4	Icterus	–	0.97
37	30.4	1310	3	RDS, hyperbilirubinaemia	+	1.32
38	28.0	1050	3	RDS	–	1.28
39	32.0	1735	4	RDS, pneumonia	–	1.72
40	33.0	1985	3	RDS, hyperbilirubinaemia	–	1.77
41	33.0	1615	4	Hyperbilirubinaemia	–	1.26

[a] GFR measurement was repeated on day 11
[b] The diagnoses small for gestational age and prematurity are not mentioned in the diagnostic list

compared using the paired Student's *t*-test. A P level of less than 0.05 was considered as significant. The relationship between GA and GFR (ml/min or ml/min·kg) was calculated using linear regression.

Results

The reliability of the inulin determination

The reliability of our test system was evaluated in various ways.

The hydrolysis step. Hydrolysis was complete between 5 and 15 min at 70°C. An incubation time up to 60 min did not influence the results. Glucose and fructose remained stable under these conditions. Although hydrolysis at room temperature is slow, a few percent per hour, blank values were determined immediately after deproteinization. These values varied between 1.6 and 48.4 mg/l "inulin" (average 19.3 mg/l, $n = 73$) and are well above the lowest detection limit of the analysis (4–5 mg/l). The recovery at the 200 and 500 mg/l levels was 101% ± 5.8% and 103% ± 4.4% respectively.

The infusion period. Since a reliable inulin clearance depends on a stable plasma concentration in an equilibrium situation, we controlled the validity of our infusion time. In 9 infants infusion was continued for 30 h and serum inulin concentrations

Table 2. Inulin plasma levels in nine patients after 24 and 30 h of inulin infusion (mg/l)

	24 h	30 h
1	324	393
2	337	346
3	345	318
4	279	285
5	291	248
6	356	349
7	272	302
8	355	372
9	184	175

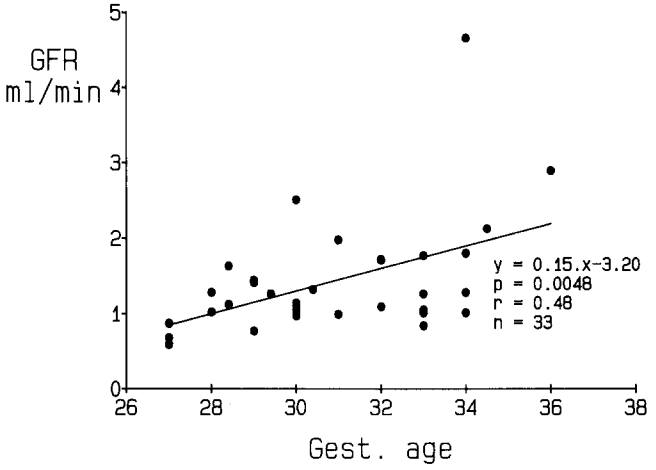

Fig. 1. The relationship between glomerular filtration rate (GFR; ml/min) and gestational age

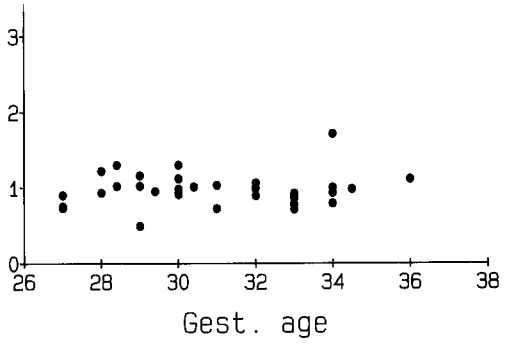

Fig. 2. The relationship between GFR (ml/min·kg) and gestational age

determined after 24 and 30 h (Table 2). There was no statistically significant difference between the two sets of values, thus reflecting stable plasma concentrations.

Patients

The effect of GA on GFR was evaluated using data from 33 infants, their GFR being measured on day 3, 4 or 5. Although interindividual variations in calculated GFR were rather large, we found a significant positive correlation ($r = 0.48$, $P = 0.0048$) between GFR (ml/min) and GA (weeks) (Fig. 1). When expressed in ml/min·kg (Fig. 2), there was no significant correlation between GFR and GA.

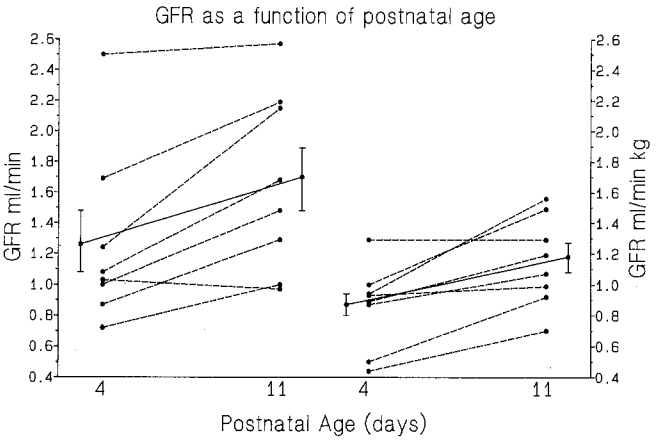

Fig. 3. The relationship between GFR and postnatal age

Table 3. Differences between patients without (group 1) and with (group 2) artificial respiration (mean ± 1 SD)

	Group 1 $N = 26$	Group 2 $N = 15$	Significance
Gestational age (weeks)	31.2 ± 2.09	29.5 ± 2.55	NS
Birth weight (g)	1396 ± 392	1363 ± 561	NS
Day of GFR measurement	4.8 ± 2.1	5.5 ± 2.8	NS
GFR (ml/min)	1.35 ± 4.2	1.42 ± 1.09	NS
GFR (ml/min · kg)	0.98 ± 0.16	0.97 ± 0.33	NS

In order to establish the effect of PA on GFR, we repeated GFR measurements on day 11 in 8 infants previously determined on day 4 or 5. A significant increase in GFR was present. The GFR increased from 1.28 ± 0.57 ml/min to 1.68 ± 0.57 ml/min ($P < 0.007$). This increase was also present when GFR was expressed relative to BW (0.88 ± 0.23 ml/min · kg to 1.18 ± 0.28 ml/min · kg; $P < 0.008$) (Fig. 3).

When GFR was expressed as a function of post-conceptional age (GA + PA) data were comparable with those in Figs. 1 and 2. The GFR (ml/min) increased significantly [GFR = 0.151 × (GA + PN) − 3.35; $r = 0.48$; $P = 0.0015$; $N = 41$]. Again, no increase was present when GFR was expressed relative to BW.

To establish the effect of artificial ventilation on GFR in preterm neonates, we compared the GFR of those needing artificial ventilation ($N = 15$) with that of neonates breathing spontaneously ($N = 26$) (Table 3). No significant difference in GA, BW or in day of GFR measurement was present. The GFR, either absolute or relative to BW, did not differ significantly between the two groups (0.98 ml/min · kg ± 0.16 vs 0.97 ml/min · kg ± 0.33).

Discussion

The traditional inulin clearance, used for the first time in the early 1930s [24, 25] is considered to be the gold standard for determination of GFR. Inulin is a fructose polysaccharide with a mean molecular mass of about 5 kDa, is not meta-

bolised by the body and is completely filtered by the glomeruli. The technique has proven to be useful in adults, children, as well as in preterm neonates [10].

The measurement of creatinine clearance can be considered as an alternative for inulin clearance. It depends on the success of urine collection and on bladder emptying. However, serum creatinine levels during the 1st day of life are partly dependent on maternal serum levels [22], and alter rapidly. Moreover, there is evidence from animal experiments that tubular reabsorption of creatinine is possible in the very young animal [3, 11], although it is uncertain whether this latter finding applies to the preterm newborn.

The single injection technique for measuring GFR has been practised by Broberger and Aperia [6] using inulin and Svenningsen [27] using polyfructosan. Coulthard and Ruddock [8], however, demonstrated that the use of single injection techniques can lead to an overestimation of up to 10% of the real value of GFR. Only in a few patients trustworthy results can be obtained by this technique. These data are in accordance with those of Fawer et al. [13].

Continuous infusion without urine collection may be an alternative method to measure GFR. After an equilibration period the amount of infused inulin will be equal to the amount excreted by the kidneys. This equilibration time will depend on the plasma half life ($t_{1/2}$) and on the level of GFR itself. $t_{1/2}$ in neonates has been reported to be greater than 4 h [8]. This long $t_{1/2}$ in neonates can be attributed to the combination of a low GFR and a large extracellular fluid space, wherein inulin is distributed [15]. After an infusion period of five times the $t_{1/2}$ the inulin plasma levels reach a value with 3% of the steady state concentration. This explains why 24-h infusion is needed in preterm infants. A short interruption during infusion requires a fairly long period before a stable plasma level is achieved.

Another complicating factor is the large fluctuation of serum inulin blanks in neonates due to variations in "fructose-like" substances. We found serum blank values up to 50 mg/l, independent of exogenous administered inulin. This may lead to an inacceptable inaccuracy in calculation of GFR. By means of our stepwise procedure we were able to eliminate this problem, as is demonstrated by recoveries of 101% and 103% after addition of exogenous inulin to randomly-chosen plasma samples. We utilized the latter technique in our study.

Our data demonstrate that GFR rises during development in two different ways. Firstly, there is an effect of increase in BW as indicated by the correlation between GFR, expressed in ml/min, and GA (Fig. 1) and the lack of correlation between GA and GFR expressed in ml/min · kg. Secondly, there is a further increase in GFR postnatally (Fig. 3). This increase appears to be independent of an increase in BW. This latter finding, previously demonstrated by Fawer et al. [14] was criticized by Coulthard [9], who considered the observed increase in GFR relative to body weight during early postnatal life as an artefact. This was, in his opinion, related to a temporary postnatal decrease in BW as it was absent when GFR was expressed per kilogram of so-called projected weight. This is the weight obtained by a parallel projection from the birth weight along the centiles of Gairdner and Pearson [16], as if babies had continued to grow at a rate observed during intrauterine life. We found an increase in GFR of 30%; much more than can be expected to occur as a consequence of BW changes. BW in our 8 neonates, was not significantly different at day 4 and day 11.

From animal experiments there is evidence that GFR increases postnatally independent of an increase in BW. This increase appears to depend on haemodynamic changes in the kidney. An increase in renal blood flow (RBF) has been described [17, 26]. More recently, it was demonstrated in sheep that a postnatal increase in GFR without changes in RBF can occur, probably depending on intrarenal redistribution of blood flow resulting in a rise in glomerular plasma flow in outer cortical nephrons [23].

The GFR in patients with ventilatory support was not significantly different from that of unaided infants (Table 3). This indicates that artificial ventilation had no significant effect on the level of GFR.

However, 13 of the 26 neonates breathing spontaneously had respiratory problems, as for example respiratory distress dyndrome (RDS), known to decrease GFR [7, 18, 28]. We also compared the artificially ventilated newborns with those without known respiratory diseases. Again no significant differences were found. This contrasts with the data of Leslie et al. [21], who found a negative effect of artificial ventilation on glomerular filtration using creatinine clearance. In their study the reported values for creatinine clearance are surprisingly low for infants needing artificial ventilation as well as for those breathing spontaneously. The observed changes in GFR in neonates with RDS and those needing artificial ventilation, reported in the literature, are probably due to a combination of negative influences: hypoxaemia, hypercapnia and variations in systemic blood pressure. As an example, we have shown in the newborn rabbit model a significant decrease in GFR related to acute hypercapnic acidosis [19].

In conclusion, we found that the 24-h inulin infusion technique is sufficiently accurate to evaluate the development of GFR in the preterm infant. The GFR of the newborn rises in two different ways during development: firstly, an increase during gestation, associated with body growth; secondly, a postnatal increase independent of an increase in BW. We were unable to demonstrate a significant effect of artificial ventilation upon the GFR in preterm infants.

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