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Postnatal development of renal function during the first year of life*

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Abstract. Several aspects of renal function vary considerably during the 1st year of life and differ markedly from the equivalent values in the adult. Glomerular filtration rate (GFR) increases little, prior to the time an infant reaches a conceptional age of 34 weeks, the point in renal development from which the absolute GFR (ml/min) increases gradually to mature values when linear growth is completed during adolescence. GFR corrected for body size is not comparable with adult normal values until after 12 months of age; therefore, whether GFR is estimated from S_{cr} or measured by timed urine collection, there is no easily recalled range of normal values for infants. One must know the changes in the renal function of normal infants that take place following birth during the 1st year of life. Despite several attempts to do so, renal function during the 1st year of life cannot be assessed from urine flow rate. A urine flow rate of less than 1 ml/kg per hour may be normal and appropriate and may not be harmful either to preterm or full-term infants with normal GFR. Impaired concentrating ability of the neonatal kidney is probably of no clinical significance in all but the most extreme circumstances and is not a major factor in an infant becoming dehydrated, developing hypernatremia or being at greater risk of acute renal injury. Acid-base status in infants must be interpreted appropriately to know when alkali therapy should be introduced to avoid growth failure secondary to true metabolic acidosis. When plasma renin activity is measured in the infant with renal failure of hypertension, one must compare the result with the normal range of values related to postnatal age of normal infants.

Key words: Renal function – Glomerular filtration rate – urine flow rate – Sodium – Acid-base balance – Plasma renin activity

Introduction

The assessment of renal function during the 1st year of life is fraught with greater difficulty than at any other age. Five distinct differences which account for most of the confusion in interpreting measurements of renal function during the newborn period and infancy are glomerular filtration rate (GFR), urine flow rate/urinary concentrating capacity, renal handling of sodium, acid-base balance and plasma renin activity (PRA). Each of these differences will be reviewed in summary fashion.

Glomerular filtration rate

Barnett [1] was the first to demonstrate that GFR, measured as inulin clearance, was lower in infants compared with normal adult values even when allowances were made for differences in body size. Later, Smith [2] summarized in his monograph all reported measurements of GFR for premature and full-term infants during the first months of postnatal life; he concluded, as did Barnett, that GFR in the infant could not be corrected for body size and compared predictably with the adult range of normal values (90–140 ml/min per 1.73 m^2). This point was more clearly illustrated by Aperia et al. [3], who compared GFR, corrected to 1.73 m^2 body surface area (BSA), with post-

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natal age plotted on a logarithmic scale. Corrected values for GFR in full-term infants did not change during the 1st month of life, i. e., GFR and BSA increased proportionately. Between the 1st and 13th months, hower, GFR increased more rapidly than BSA, and at the end of the 1st year of life, GFR (ml/min per 1.73 m^2) was comparable with normal adult values.

Serum creatinine concentration (S_{cr}) is the most frequently used measurement for impaired renal function in infants. Determinations of GFR irrespective of the method used are required much less frequently. In the newborn infant, S_{cr} is nearly identical to that in the mother [4]. In infants born at term, S_{cr} decreases by approximately 50% during the 1st week of life and decreases further to a "normal" value of 0.35–0.40 mg/dl over the next 2 months of life [5]. No further change in S_{cr} occurs in normal infants during the remainder of the 1st year. Creatinine production and urinary creatinine excretion are equivalent; these values approximate 15 mg/kg per day in infants born at term [5]. The same study documented that GFR increased from a mean value of 6.6 ml/min (1.9 ml/min per kilogram or 50.6 ml/min per 1.73 m^2) at 5–7 days of age to 21 ml/min (2.4 ml/min per kilogram or 86 ml/min per 1.73 m^2) at 12 months. After the 1st year of life, lean body mass and creatinine production increase more rapidly than GFR, so that S_{cr} increases gradually until a normal adult value of 1.0–1.5 mg/dl is reached during adolescence.

To facilitate the clinical assessment of GFR in infants, Schwartz et al. [5] derived a formula in the same fashion as they had done previously for children [6]. GFR corrected to 1.73 m^2 BSA after the 1st week of life for infants born at term could be estimated by factoring the length of the infant, measured in centimeters, by a constant of 0.45, which reflects lean body mass; the result is then divided by the S_{cr} expressed in mg/dl.

$$\text{GFR (ml/min per 1.73 m}^2) = 0.45 \times \text{L (cm)} / \text{Pcr (mg/dl)}$$

The disadvantage of this or any other estimate of GFR during the 1st year of life is that GFR does not correct to a range of normal values; therefore, a table of normal values must be referred to when GFR is assessed in infants. Furthermore, the accuracy of this method depends on the validity of measurements of body length and Scr.

The same principles do not apply to infants born prematurely. In preterm infants studied at birth and during postnatal life, GFR did not increase prior to 34 weeks following conception. When a conceptional (gestation + postnatal) age of 34 weeks had been reached, infants born at an earlier stage of development exhibited a rapid increase in GFR similar to that of infants born at term and studied during the 1st week of life [7]. This nonlinear relationship has been confirmed subsequently [8, 9].

The pattern of change in GFR with conceptional age corresponds to the presence of the nephrogenic zone in the cortex of the developing human kidney. The increase in GFR at 34 weeks from conception corresponds to the period of rapid disappearance of the nephrogenic zone [10]. This pattern of rapid change in GFR at or around the time when glomerulogenesis has been completed appears to be characteristic of most, if not all, mammalian kidneys and occurs in utero in sheep and postnatally in the dog and the rat. This pivotal time in renal functional development has important implications for utilizing S_{cr}, or changes in S_{cr} to estimate GFR in infants born prior to 34 weeks' gestation. As reported by Stonestreat and Oh [11], values for S_{cr} in preterm infants do not decrease by 50% during the 1st week of life as do those in term infants. Equivalent decreases may take 2–3 months in the preterm infant. Personal observations on S_{cr} in preterm infants support many of the findings of Stonestreet and Oh [11], but when GFR in these same preterm infants of different gestational ages was compared with postnatal age, there was no predictable relationship. When serial determinations of S_{cr} in the same infants were compared with postnatal age, S_{cr} in very preterm infants actually increased during the first 10 days of life, while infants born at 33–34 weeks' gestation exhibited a decrease in S_{cr} like full-term infants.

On the other hand, when the S_{cr} of these same infants were compared only with conceptional age, regardless of postnatal age, a pattern of gradually decreasing S_{Cr} was observed. When S_{Cr} studied in a serial fashion was compared, it could be seen that regardless of the level of S_{Cr} at birth, there was a gradual decrease prior to a conceptional age of 34 weeks, but after 34 weeks, at a time when GFR was increasing in a rapid fashion, the decrease in S_{Cr} was more rapid and similar to that observed in older infants during the 1st week of life. Therefore, whether renal function is interpreted as changes in S_{Cr} or in GFR, the infant suspected of abnormal renal function should be studied in a serial fashion, and values derived compared with normal values in infants of corresponding conceptional ages.

Often an infant with respiratory distress syndrome, treated by positive pressure ventilation, will exhibit decreased GFR or an acute increase in S_{Cr}. An increase in intrathoracic pressure caused by the ventilator or by pneumothorax decreases cardiac output [12]. The infant's kidney, like that of the adult, responds to a decrease in cardiac output by renal vasoconstriction, decreased GFR and salt and water conservation [13]; this cause of prerenal failure is reversible when intrathoracic pressure can be reduced, and the diagnosis of chronic impairment of renal function in such infants should be made cautiously.

Urine flow rate/urinary concentrating capacity

In the absence of a reliable and easily interpretable measurement of GFR in the neonate, many clinicians have resorted to estimating renal function by urine volume. An arbitrarily chosen urine flow rate equal to or more than 1 ml/h per kilogram has been accepted widely as "adequate renal function". Many years ago, when preterm infants were given little or no fluid for several days following birth, urine volume was relatively greater in preterm than in full-term infants [14]. In those given no fluids for 72 h after birth, preterm infants excreted approximately 1 ml/h per kilogram of urine, which was twice that of the infants born at term, whose urine volume was approximately 0.3 to 0.5 ml/h per kilogram. Infants rarely, if ever, exhibited any detrimental effect on the kidney by this kind of fluid deprivation. When water was provided to other infants of comparable maturity on the 2nd and 3rd days of life, their urine volume was approximately 2–3 times greater than that of their thirsted counterparts. It must be pointed out, however, that insensible losses in these infants were minimal; unlike those treated today under radiant warmers and lights, which may increase evaporative water losses as much as 9 ml/kg per hour [15], fluid deprivation in these infants could be disastrous.

The basis for concern over maintaining urine flow rate originated with the knowledge that the neonatal kidney cannot concentrate the urine to the same extent as the adult kidney [16]. Moreover, renal injury from acute insults like hypoxia and nephrotoxic drugs is minimized when the flow of tubular fluid is maintained in experimental animals and man. When newborn infants were deprived of fluids for 72 h, an endogenous vasopressin response was observed [14]; in fact, the infants achieving the highest urinary osmolarities at the end of 72 h were the least mature of them. Aperia et al. [17] reported no effect of increasing fluid intake on neonatal GFR, only an increase in urine flow rate and sodium excretion. It was interesting to note that the fraction of glomerular filtrate excreted in the urine, calculated as urine flow rate divided by GFR (V/GFR), was doubled, and urinary osmolarity was halved in infants given additional fluid intake.

What is fractional urine flow rate or V/GFR? This term is used to express the fraction of the volume of glomerular filtrate present in Bowman's space that is not reabsorbed along the nephron and reaches the final urine. When newborn infants were studied on the 1st day of life and V/GFR was compared with gestational age, those born prior to 34 weeks were observed to excrete approximately 10% of the volume of glomerular filtrate in their urines (unpublished data). After 34 weeks, V/GFR decreased to be only approximately 3% in infants born at term. This high fractional rejection of glomerular filtrate by very preterm infants is characteristic of other mammalian fetuses; Robillard et al. [18] observed V/GFR in the sheep to be 25% in very preterm fetuses and 15% in fetuses closer to term. What, then, is the value of calculating "minimally safe urine flow rates" to estimate renal function in newborn infants? If, by comparison, the adult weighing 60 kg, whose GFR is 125 ml/kg per hour, has a urine flow rate of 1 ml/kg per hour, only 0.8% of the volume of glomerular filtrate would be excreted in the urine. In the infant born at term and weighing 3.5 kg, whose GFR is 80 ml/kg per hour, a urine flow rate of 1 ml/kg per hour would represent 1.3% of the volume of glomerular filtrate excreted in the urine. In the extreme example, an infant born at 25 weeks and weighing 750 g, whose normal GFR is 20 ml/kg per hour, would have to excrete 5% of glomerular filtrate to satisfy the clinician whose goal is to maintain urine volume at a "safe" value of equal to or above 1 ml/kg per hour. Such a requirement cannot be considered safe for preterm neonates, it is unphysiological and is an excessive demand to make on the neonatal kidney.

What is the clinical relevance of the newborn infant's inability to concentrate his urine to an extent comparable with that in the mature kidney? While the statement is true that in response to water deprivation or vasopressin administration the newborn kidney cannot concentrate urine to 1200 mosmol/l as the adult kidney can, the neonate can concentrate urine to 700 mosmol/l [16], a limitation not considered dangerous to water balance in the adult. When explaining why the maxi-

mal urinary concentrating ability of the neonate is less than that of the adult, there are many factors to consider. Edelmann et al [16] suggested that the type and amount of dietary protein provided for infants in the diet produced insufficient urea for renal tubular absorption to increase medullary tonicity. Infants fed a very high protein diet could be made to concentrate urine at a higher rate than infants fed normally, but not to the same degree as the adult. Moreover, the amount of protein required to do this could not be justified.

Other explanations for the relative lack of concentrating ability in the immature kidney have focused upon anatomical differences, specifically the relatively short loops of Henle observed in the neonatal kidney. Recent interest has focused on the role of prostaglandins, and Dunn [19] has summarized their impact on the urinary concentrating mechanisms. PGE_2 inhibits NaCl transport in the thick ascending limb to decrease the amount of NaCl added to the medullary interstitium for gradient generation. Moreover, PGE_2 in the collecting tubule interferes with urea reabsorption to make less of it available for the medullary gradient and antagonizes vasopressin-mediated water flow across the tubular epithelium. Finally, prostacyclin produced by the vascular endothelium increases medullary blood flow to wash out the medullary gradient. Since prostaglandin synthesis by the neonatal kidney and blood vessels is increased over that of the adult [20], it is quite possible that most developmental differences in concentrating ability can be explained by the presence of increased prostaglandin production.

Renal handling of sodium

The renal handling of sodium has provided the rationale for many clinical and laboratory studies of renal function during development. Dean and McCance [21] reported that infants given a 40% NaCl solution did not excrete the load in the same way as adults. Of interest is that sodium was not measured during those studies, but the authors' conclusions about sodium excretion were extrapolated from measurements of urine volume. In clearance studies of full-term infants, Aperia et al. [22] concluded that distal sodium reabsorption, calculated as free water clearance, was unlimited. Comparison studies of young adults showed that distal tubular sodium reabsorption was limited relatively to that in the newborn. Subsequent studies of premature infants by the same authors [23] confirmed the same unlimited capacity of the distal nephron to reabsorb sodium. The major criticisms of those studies have been that the infants may not have been studied during maximal water diuresis, which is a requirement for the validity of clearance studies, and that the distal delivery of sodium may not have been sufficient to test the maximal capacity of the distal nephron to reabsorb sodium. The implication of these studies was, however, that hypernatremia would result in an infant given excess sodium, if renal capacity to excrete sodium was limited. Anecdotal experiences of accidental deaths in infants whose formula preparation had been with salt instead of dextrose supported this notion. However, preterm infants had been noted previously to excrete more NaCl in their urine than full-term infants [14], and negative sodium balance was characteristic of preterm infants [24]. Furthermore, clinical experience with newborn infants would suggest that hyponatremia and salt wasting are observed more frequently than hypernatremia and salt retention. Both the inability to excrete a sodium load and the capacity of the kidney to conserve sodium in the face of hyponatremia have been used as arguments to propose that the newborn kidney is functionally immature. What these two opposing views suggest, however, is that neither is, by itself, a marker of tubular maturation.

Subsequently Siegel and Oh [25] have described that infants given fluids following birth exhibited a negative sodium balance prior to 34 weeks' gestation, while positive sodium balance was observed in more mature infants. These authors also reported that the fractional excretion of sodium was higher in preterm infants and characteristically was above 1%; therefore, the interpretation of FE_{Na} values in preterm infants suspected of acute renal failure is made more difficult. Sulyok et al [26] reported that preterm infants studied for the first 6 weeks of life exhibited negative sodium balance during the first 2 weeks, but on identical sodium intake a positive sodium balance was observed after the 2nd week of life. When the distal delivery of sodium and its reabsorption were re-examined developmentally during maximal water diuresis, Rodriguez-Soriano et al. [27] found that distal sodium delivery was higher at birth and decreased during the 1st year of life to become similar to that of the adult. In a further study, Rodriguez-Soriano et al. [28] demonstrated in newborn infants at 7 days of age that there was indeed a limit to the capacity of the distal nephron to reabsorb sodium when a critical value of distal sodium delivery was exceeded. When we compared distal sodium reabsorption in infants studied during the 1st week of life with distal so-

dium delivery or V/GFR, we observed that regardless of the maturity or the postnatal age of the infant, sodium reabsorption, measured as free water clearance during water diuresis, reached a maximum when distal sodium delivery or V/GFR approached 15% of filtered load [29]. In studies of the dog [30] and man [31], a linear relationship between changes in V/GFR and FE_{Na} was observed. This implies that for any factor which increases V/GFR, such as volume expansion, a high rate of fluid administration or diuretic therapy, FE_{Na} will increase.

Acid-base balance

Metabolic acidosis is another marker of renal failure because the kidney is responsible not only for the excretion of hydrogen ion but also for the reabsorption and generation of new bicarbonate. Edelmann [32] observed that preterm infants had values for urinary pH that were higher during the 1st than the 2nd week of life. Some interpreted this study to represent a transient impairment of hydrogen ion secretion in the neonate and an impaired ability to excrete an acid load. It was later determined by Schwartz et al. [33] that net acid excretion in preterm infants was normal compared to the adult. These investigators also observed that the serum bicarbonate levels estimated from total CO_2 were low in preterm infants at birth and increased with postnatal age; the mean value was 17 mM/l. Edelmann et al. [34] found age-related differences in the renal threshold for bicarbonate. This meant that serum bicarbonate concentration was normally lower in the infant than the child. Serum bicarbonate in infants born at term is typically 19 to 21 mM/l; by 12 months of age it averages 21 to 24 mM/l, while the adult normal range is 26 to 28 mM/l. When assessing the acid-base status of the infant, one must remember not only these differences, but also that the preterm infant normally has a relative metabolic acidosis when compared even with the full-term infant. It should be noted further that in studies of humans and animals, volume expansion can decrease both the renal threshold for bicarbonate and the serum bicarbonate concentration, and increase the urinary pH [35, 36]. Therefore, efforts to maintain urine flow rate equal to or above 1 ml/kg per hour or to increase blood pressure with fluid boluses may also decrease the renal threshold for bicarbonate and lower plasma bicarbonate concentration and aggravate metabolic acidosis.

Plasma renin activity

The normal developmental pattern of change following birth has recently been studied in detail. PRA is often measured in infants with hypertension or renal fialure. At birth, PRA in full-term infants is 10–12 ng/ml per hour; it decreases during the 1st year of life to 5 ng/ml per hour; the adult normal value of equal to or above 1 ng/ml per hour is not reached until about 6 years of age [37]. Most stimuli of renin release are mediated through PGE_2 and PGI_2 which, like PRA, are increased in the neonate. Kaapa et al. [38] found plasma prostacyclin concentrations to be highest at birth and to decrease over the 1st year of life. The postnatal changes in PRA reported by others are temporally related to changes in plasma prostacyclin concentrations during the 1st year of life. Moreover, the urinary excretion of PGE_2 and 6 Keto PGF_{1a} is relatively greater in infants born prior to 30 weeks and decreases with continued maturation [39]. Even in infants born at term, values are greater than those measured in older children. Seyberth et al. [40] administered indomethacin to premature infants with patent ductus arteriosus and noted both PRA and prostaglandin excretion to decrease. Moreover, urine flow rate decreased and urine osmolality increased in their infants after prostaglandin synthesis inhibition. Therefore, a causal relationship between increased PRA and prostaglandin production in the neonate was suggested.

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