Renal Interlobar Artery Parameters with Duplex Doppler Sonography and Correlations with Age, Plasma Renin, and Aldosterone Levels in Healthy Children

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OBJECTIVE. The objectives of this study were to compare and make correlations between age and Doppler parameters of the interlobar arteries, including synchronously obtained plasma renin and aldosterone levels and to obtain new normative data regarding acceleration time in healthy children from neonates to 16 years.

SUBJECTS AND METHODS. One hundred sixty-nine healthy children (72 girls and 97 boys) were classified into four groups: group 1 (< 1 year; $n = 34$), group 2 (range, 1–6 years; $n = 48$), group 3 (range, 6–12 years; $n = 50$), and group 4 (range, 12–16 years; $n = 37$). Blood samples from the renin and aldosterone were collected in the morning after bed rest and fasting. The resistive index (RI), pulsatility index (PI), and the acceleration time of the renal interlobar arteries with duplex Doppler sonography, including both kidney longitudinal lengths with gray-scale sonography, were evaluated. One-way analysis of variance with the least significant difference post-hoc test and Pearson's correlation test were used to compare the differences between groups and to make correlations, respectively. An independent-sample *t* test was used to evaluate the differences between all parameters based on sex and to compare the left and right kidney longitudinal lengths in each group.

RESULTS. The RI, PI, and acceleration time were statistically significant in between-group comparisons. Only in group 4 was acceleration time not statistically significant compared with groups 2 and 3. Plasma renin levels were significantly higher in group 1 compared with groups 2 ($p < 0.03$) and 4 ($p < 0.0001$); in group 2 compared with group 4 ($p < 0.05$); and in group 3 compared with group 4 ($p < 0.01$). The plasma aldosterone levels were significantly higher only in group 1 compared with groups 2 ($p < 0.001$), 3 ($p < 0.008$), and 4 ($p < 0.0001$). The RI correlated linearly with the PI, plasma renin levels, and aldosterone levels and correlated inversely with acceleration time. Age had a negative correlation with the RI, PI, plasma renin levels, and aldosterone levels and correlated positively with acceleration time. There were no statistically significant differences between all parameters based on sex and no significant difference found between the right and left kidney longitudinal lengths in each group.

CONCLUSION. The RI in children up to 54 months old is higher than in adults. Therefore, the adult mean renal RI criterion of 0.70 should be applicable to children 54 months old and older. We showed that the age dependency of the RI was directly related to that of plasma renin and aldosterone levels in healthy children in whom Doppler parameters and blood analysis were evaluated synchronously.

Keywords: aldosterone, Doppler sonography, kidney, pediatric radiology, renin, sonography

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Duplex Doppler sonography provides a high-quality and noninvasive display of flow in the renal and intrarenal blood vessels and enables measurements of flow parameters that may have importance in several kidney diseases [1–9]. To recognize abnormal renal Doppler findings in these kidney diseases, the range of the normal values for intrarenal arterial Doppler parameters, such as the resistive index (RI), pulsatility index (PI), and acceleration time must be established. Although the RI is affected by multiple factors, such as in diseases causing the pressure differential between systole and diastole [10], RI is one of the Doppler parameters that provides information about arterial impedance. The RI has multiple applications [1–9]. Theoretically, the RI and PI express vascular resistance. Since PI involves mean velocity, it can reflect flow better than the RI [11]. The PI has been useful in the detection of acute rejection of a kidney allograft and acute tubular necrosis but not chronic rejection [12]. Acceleration time has been useful for the detection of renal artery stenosis, acute renal failure, and transplant rejection [8, 13–15].

It has been shown that renal vascular RI changes with age [8, 16–20]. In one study [16], the age dependency of the renal RI and renal vascular resistance was connected to change in active plasma renin levels, similar to another study [17] where it was connected to plasma renin activity (PRA). However, these studies were not synchronously evaluating the relationship between the normal renal RI and the levels of active renin or plasma renin activity in the same study group.

The purpose of the present prospective study was to compare and make correlations between patient age and the Doppler parameters of the interlobar arteries, including synchronously obtained active plasma renin and aldosterone levels, and to find any causal link with active plasma renin or other parameters that cause the decline in RI with age. Our study also aimed to establish new normative values for the acceleration time in healthy children from neonates to 16 years.

Subjects and Methods

Between January and September 2003, 169 healthy children (72 girls and 97 boys) who had a routine physical checkup at the department of pediatrics were evaluated in the department of radiology. Color Duplex sonography was performed in the interlobar arteries of both kidneys. Although routine physical checkup includes children up to 7 years old at our institute, children older than 7 years were mainly older brothers and sisters of patients in the checkup group. The inclusion criteria for the study were the absence of clinical or laboratory pathologic findings with normal urinalysis and complete blood count; normal B-mode sonography findings in both kidneys; and absence of any systemic disease, hypertension, and chronic or metabolic disease history. Informed consent was obtained from the parents of all patients. This study was approved by the hospital ethics committee.

Children in our study were classified in four groups. Group 1 included 34 children ranging in age from 5 days to 1 year (mean age, 4.9 months), group 2 included 48 children between 1 and 6 years, group 3 included 50 children between 6 and 12 years, and group 4 included 37 children between 12 and 16 years.

Children were evaluated in the prone position with duplex Doppler sonography (HDI 5000 and HDI 3500, Philips Medical Systems) after approximately 3 hr of fasting. The scanners were equipped with convex 2- to 5-MHz and linear 4- to 7-MHz probes. The ultrasound gel was warmed with a heated towel before sonography. The shape, size, and echogenicity of the kidneys were evaluated before performing Doppler sonography of the interlobar arteries. The Doppler sample volume was positioned after color positioning of the interlobar arteries. The Doppler angle was kept below 60° with respect to the long axis of the artery. The pulse repetition frequency was set to avoid aliasing, and the wall filter was optimized as low as possible to detect slow diastolic flow. The children, if possible, were instructed to suspend respiration during Doppler recordings. For neonates and young children, the mother was lying near her child and duplex Doppler sonography was performed when the child was calm and breathing quietly. Recordings were obtained from the upper, middle, and lower third of the kidney in three different vessels until at least three adequate consecutive spectral waveforms were obtained. The same person (with approximately 11 years of experience with Doppler examinations) performed all sonographic studies together with data analysis. The peak systolic velocity (PSV), end-diastolic velocity (EDV), RI, PI, and acceleration time were measured and calculated automatically by the spectral analyzer of the sonographic system (Fig. 1). All measurements obtained from the interlobar arteries of the upper, middle, and lower third of each kidney were averaged. The left and right kidneys had similar patterns and data in each patient. Sedation was not used.

To calculate resting active plasma renin and aldosterone levels, the venous blood samples were taken in the morning. The venous line was opened 1 hr before being placed in the supine position to prevent traumatic venipuncture and stress during blood collection. The venous line was closed by a tap and a small amount of dextrose solution (0.5 mL each time) was given to prevent blood clotting. During 1 hr in the supine position to calm the infants and toddlers, their mothers lay beside them. All children fasted for at least 3 hr before sample collection. After blood collection for renin, the samples were centrifuged at room temperature and stored frozen immediately with dry ice at −20°C or below if not tested within hours of primary collection. The use of dry ice was important to prevent cryoactivation of prorenin at 2–8°C [21]. For aldosterone, dry ice is not necessary. Blood for measuring aldosterone levels should be frozen at −20°C or lower in a deep freeze. During the time of assay, the frozen samples were warmed quickly in 37°C water and then the levels of active plasma renin and aldosterone were calculated.

Active plasma renin and aldosterone levels were measured with a DSL-25100 ACTIVE Renin IRMA Kit and DSL-8600 ACTIVE Aldosterone Coated-Tube Radioimmunoassay Kit (Diagnostic Systems Laboratories), respectively.

The results are reported as mean ± SD. The normal distribution of the values for each parameter was determined by the Kolmogorov-Smirnov test. Between groups, differences were compared by one-way analysis of variance with a least significant difference post-hoc test. The correlations were evaluated with Pearson's correlation test. An independent-sample *t* test was used to evaluate the differences between all parameters based on sex and to calculate any difference between the left and right kidney longitudinal lengths in each group. A *p* value of less than 0.05 was considered statistically significant.

Results

The Doppler parameters of the interlobar arteries and active plasma renin and aldosterone levels in healthy children are shown in Table 1. The correlations between the parameters in 169 healthy children are presented in Table 2.

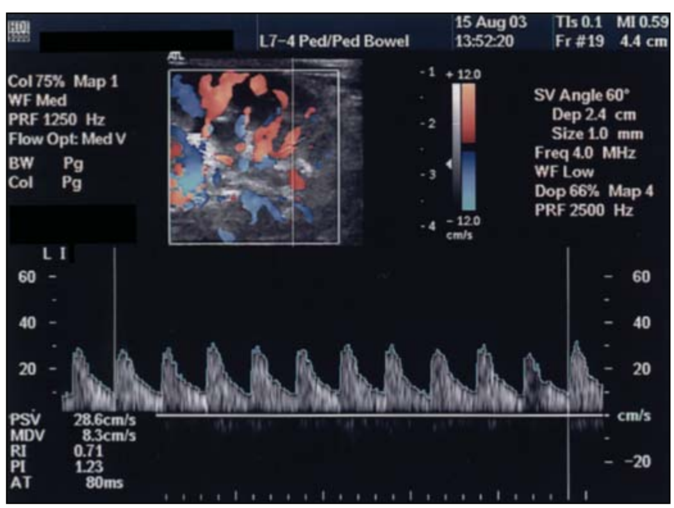

Fig. 1—3-month-old healthy female infant with duplex Doppler sonography evaluation of interlobar artery from inferior pole of left kidney (LI = left inferior, RI = resistive index, PI = pulsatility index, PSV = peak systolic velocity, MDV = minimum diastolic velocity, AT = acceleration time).

TABLE 1: Interlobar Artery Parameters with Duplex Doppler Sonography and Active Plasma Renin and Aldosterone Levels in 169 Healthy Children (Neonates to 16 Years)

Group (*n*)	RKL (cm)	LKL (cm)	Peak Systolic Velocity (cm/sec)	End-Diastolic Velocity (cm/sec)	Resistive Index	Pulsatility Index	Acceleration Time (msec)	Active Plasma Renin Level (pg/mL)	Plasma Aldosterone Level (pg/mL)
1 (34)	4.96 ± 0.72	5.09 ± 0.69	40.1 ± 10.5	10.9 ± 2.50	0.72 ± 0.03	1.27 ± 0.20	71.0 ± 21.5	23.4 ± 21.3	248 ± 138
2 (48)	6.76 ± 0.63	7.04 ± 0.62	43.0 ± 11.0	14.8 ± 4.43	0.65 ± 0.04	1.10 ± 0.16	89.2 ± 32.4	17.2 ± 9.4	167 ± 112
3 (50)	8.28 ± 0.63	8.51 ± 0.64	46.3 ± 11.9	17.9 ± 5.15	0.61 ± 0.04	1.00 ± 0.13	103.0 ± 26.5	18.5 ± 9.7	181 ± 100
4 (37)	9.73 ± 0.66	9.94 ± 0.71	47.0 ± 10.9	19.1 ± 4.80	0.59 ± 0.03	0.96 ± 0.10	99.7 ± 23.0	11.8 ± 7.6	146 ± 98

Note—All data are mean ± SD. RKL = right kidney longitudinal length; LKL = left kidney longitudinal length.

Age was found to correlate inversely with RI, PI, active plasma renin levels, and aldosterone levels and correlate linearly with acceleration time. A positive correlation was found between RI and active plasma renin and aldosterone levels and PI, respectively; there was a negative correlation between RI and acceleration time (Table 2).

There was a trend both for the right and left kidney longitudinal lengths to increase with age. This trend was significant for both kidney longitudinal lengths in all groups ($p < 0.0001$). However, in each group, no statistically significant difference was found between the right and left kidney longitudinal lengths.

The RI tended to decrease with increasing age. This trend was significant between groups 3 and 4 ($p < 0.01$) and among all other groups ($p < 0.0001$). The PI also had a tendency to decrease with age. This trend was significant between groups 3 and 4 ($p < 0.03$), groups 2 and 3 ($p < 0.001$), and between all other groups ($p < 0.0001$). The acceleration time tended to increase with age. This trend was significant between groups 1 and 2 ($p < 0.003$), groups 1 and 3 ($p < 0.0001$), groups 1 and 4 ($p < 0.0001$), and groups 2 and 3 ($p < 0.01$).

Both the active plasma renin and aldosterone levels tended to decrease with increasing age. The active plasma renin level was significantly lower in group 4 compared with groups 1 ($p < 0.0001$), 2 ($p < 0.05$), and 3 ($p < 0.01$); and in group 2 compared with group 1 ($p < 0.03$). The aldosterone levels were significantly higher only in group 1 compared with groups 2 ($p < 0.001$), 3 ($p < 0.008$), and 4 ($p < 0.0001$).

There were no statistically significant differences between age, Doppler parameters, active plasma renin, and aldosterone levels between the sexes (72 girls and 97 boys).

Discussion

To recognize abnormal renal Doppler findings in pathologic conditions in the pediatric patients [1–9], the range of normal values for intrarenal arterial Doppler parameters, such as RI, PI, and acceleration time, must be established. Once normal age-related parameters are validated, Doppler sonography is useful in the evaluation of multiple clinical abnormalities [1–9, 11–15].

The RI provides information about arterial impedance. The pressure differential between the systole and diastole was shown [10] to be a major factor influencing RI, along with the vascular compliance [22] and the cross-sectional area of the downstream vascular bed [23]. The renal RI values as measured in healthy children show a significant dependence on age [8, 16–20], although one study found no age dependence for renal artery RI in children [24]. There was negative correlation between age and RI ($r = -0.732$; $p < 0.0001$) and PI ($r = -0.556$; $p < 0.0001$) in our study. These findings are in agreement with most previous studies [8, 16–20] except for one [24]. The mean values of RI in newborns were between 0.67 and 1 in previous studies [8, 16–20] but the mean value was 0.72 in our study. The values are near or above the upper normal limit (0.70) in adults. One explanation may be related to kidney volume. It increases with age, causing an increase in vascular diameter, cross-sectional area, and then leading to decrease of RI. Gudinchet et al. [25] speculated that the arterial afterload may be smaller in a big kidney than in a small one. Other explanations may be the low or absent diastolic flow associated with low glomerular filtration rate (GFR) caused by the large number of immature glomeruli in a neonate [8, 20, 26]. After birth, GFR rises because of an increase in the mean arterial pressure and a sharp fall in renal vascular resistance, with redistribution of the intrarenal blood flow from the juxtamedullary nephrons to the superficial cortical ones during the maturation of glomeruli. The GFR of a neonate is, however, still very low compared with older children and adults. To maintain adequate GFR in the face of a low neonatal mean arterial blood pressure, the postglomerular efferent arteriolar vasoconstriction occurring in a neonate means a decrease in the arterial diameter and, thus, a cross-sectional area and an increase in the renal vascular resistance (RVR) [27]. Tublin et al. [10] also showed a linear relationship between the RI and markedly increased RVR. It seems that the hypothesis concerning the change of RI with age and high values of the RI in a neonate correlate with the physiologic parameters mentioned by Tublin et al. and Bude and Rubin [22, 23].

Our study indicates that the intrarenal vascular RI in healthy children older than 54 months is always under 0.70, a value that is a reasonable upper limit for normal intrarenal RI [28] (Fig. 2). Bude et al. [16], Kuzmic et al. [17], Lin and Cher [18], and Vade et al. [19] indicated that the renal RIs in children under 48, 72, 128, and 120 months, respectively, are elevated above the level of adult values. Our data are consistent with the data from Bude et al.; Kuzmic et al. did not examine children under 2 years of age.

Other previous studies [16–18] have also suggested that the progressive decline of RI with age is related to active plasma renin levels. These studies evaluated only Doppler parameters of the renal arteries. However, the active plasma renin was provided from another study [29] in healthy children. In our study, the possible relationship between active plasma renin levels, aldosterone levels, and RI were evaluated in the same healthy children. The decline of RI with age was correlated linearly with active plasma renin ($r = 0.158$; $p < 0.04$) and with aldosterone levels ($r = 0.222$; $p < 0.004$) in our study. The renin-angiotensin-aldosterone system is very active during the perinatal period. In the human neonate and in developing animals, PRA, renal renin gene, and renal angiotensin receptor expression are higher than in adults [27]. Fiselier et

TABLE 2: Correlations Between Parameters in 169 Healthy Children (Neonates to 16 Years)

Parameters	Age (*r*)	Active Plasma Renin Level (*r*)	Plasma Aldosterone Level (*r*)	Resistive Index (*r*)	Pulsatility Index (*r*)
Active plasma renin level	–0.231[a]				
Plasma aldosterone level	–0.219[a]	0.444[a]			
Resistive index	–0.732[a]	0.158[b]	0.222[a]		
Pulsatility index	–0.556[a]	0.085	0.094	0.798[a]	
Acceleration time	0.370[a]	–0.159[b]	–0.265[a]	–0.315[a]	–0.257[a]

[a]Correlation was significant at 0.01 level (two-tailed).
[b]Correlation was significant at 0.05 level (two-tailed).

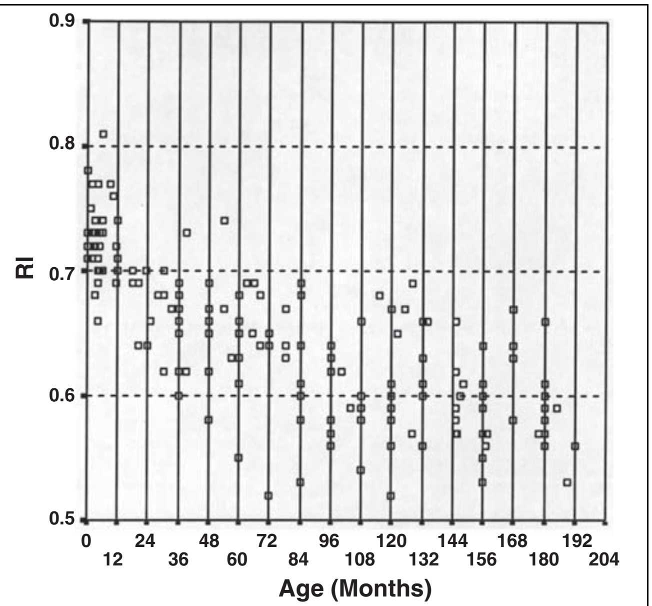

Fig. 2—Scattergram shows age dependency of mean renal resistive index (RI) plotted as mean renal RI of kidneys versus age.

al. [30] calculated PRA and aldosterone levels in the neonate as 10 ng/mL/hr and 66 ng/dL (660 pg/mL), respectively, which decreased to 4.5 ng/mL/hr and 24 ng/dL (240 pg/mL) at 12 months. In our study, the mean active plasma renin and aldosterone levels decreased until the age of 1 year, from 23.4 ± 21.3 (SD) pg/mL to 17.2 ± 9.4 pg/mL for active plasma renin levels and from 248 ± 138 pg/mL to 167 ± 112 pg/mL for aldosterone levels. Plasma renin activity is a function of the concentrations of both renin and renin substrate [29]. The PRA value in neonates in the study by Fiselier et al. and mean active plasma renin in our study were higher compared with values in a 1 year old. The aldosterone levels in the study by Fiselier et al. were higher, especially in neonates, than the values of our study. This might be a result of the method of blood collection in their study. They performed venipuncture immediately before blood collection, which may cause trauma, stress, and other significant difficulties in neonates and other age groups. Fiselier et al. revealed a negative correlation ($r = –0.67$) between age and both PRA and aldosterone levels and positive correlation ($r = 0.62$) between PRA and aldosterone levels. In our study, age was correlated inversely with active plasma renin ($r = –0.231$) and aldosterone levels ($r = –0.219$); active plasma renin and aldosterone levels had a positive correlation ($r = 0.444$) with each other. Plasma renin activity and plasma renin concentration are significantly higher in children than in adults. A lower number of angiotensin II receptors in the vessel wall of infants compared with older children might stimulate the renin-angiotensin system. The high level of PRA may also be stimulated by the lower blood pressure observed during childhood. After correction for age, the correlation between systolic or diastolic blood pressure and PRA becomes nonsignificant [30]. This might be the reason for the inverse correlation between age and active plasma renin and aldosterone levels in our study.

In our study, the mean active plasma renin, obtained particularly in group 1 healthy children, revealed a wide SD (23.4 ± 21.3 pg/mL). This variability was related to the wide spectrum of renin levels that might be present in infants under 1 year of age and the result of higher activity of renin-angiotensin-aldosterone system in a neonate. Fiselier et al. [30] reported a similarly wide spectrum of PRA as 15 ng/mL/hr in neonates under 1 month old, 7.4 ng/mL/hr in infants 1–3 months, and 4.5 ng/mL/hr in infants 3–12 months.

Acceleration time indicates the elapsed time in milliseconds from the beginning of systole to early systolic peak. Wong et al. [8] investigated the normal acceleration time in 38 healthy children from neonates to 12 years old. To our knowledge, there have been no new reported normative data with a large number of children (169 healthy children) for acceleration time. Wong et al. reported a mean acceleration time of 57 ± 21.4 msec in children 0–2 weeks, 65 ± 16.7 msec in children 2 weeks to 1 year, and 46.6 ± 19.7 msec in children 1–12 years. In our study, the mean acceleration time values were 71 ± 21.5 msec in children under 1 year, 89.2 ± 32.4 msec in children 1–6 years, 103 ± 26.5 msec in children 6–12 years, and 99.7 ± 23 msec in children 12–16 years. In our study, the mean acceleration time values were higher than those Wong et al. reported. The mean acceleration time values also showed positive correlation ($r = 0.370$) with age and negative correlation with RI ($r = –0.315$) and PI ($r = –0.257$) in our study. The positive correlation between the mean acceleration time and age may depend on a few factors. First, kidney volume, vascular diameters, and the number of vascular branches increase with age. This means the cross-sectional area increases and leads to a decrease in early systolic acceleration of the waveform (the slope of systolic upstroke), with a consequent increase in time to reach the systolic peak to acceleration time [23]. Second, the diminished vascular compliance that may occur in small vascular diameter is associated with an increase in the systolic acceleration and decrease in acceleration time [31, 32]. The mean acceleration time values and correlations with age that were revealed in our series and in the study of Wong et al. were different. This may be because Wong et al. evaluated the measurement of the potentially ambiguous waveforms in a different manner than we did. In our study, the mean acceleration time values with wide SDs were consistently greater than 70 msec, which has been considered the cutoff point for normal values [33]. Discrepant cutoff values for acceleration time are reported in the literature [13]. The reason for this may be the calculation method. In our study, acceleration time was calculated automatically by the spectral analyzer of the sonographic system to have a standard calculation method because acceleration time has been calculated different ways by many authors in the literature [34–38]. This method was chosen also to prevent intraobserver variability. However, it may be the reason for high mean acceleration time values in our study. It may be necessary for each institution to standardize the calculation method, find the mean acceleration time values for each age group, and evaluate this in clinical practice.

In conclusion, the RI in children up to 54 months old is higher than in adults. Therefore, the adult mean renal RI index criterion of 0.70 should be applicable in children 54 months and older. We showed that the age dependency of the RI is directly related to that of active plasma renin and aldosterone levels in healthy children from neonates to 16 years old in whom Doppler parameters and blood analysis were evaluated synchronously.

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