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TECHNICAL NOTE

Blood volume, colloid osmotic pressure and F-cell ratio in children with the nephrotic syndrome

JOHAN VANDE WALLE, RAYMOND DONCKERWOLCKE, PETER BOER, HANS W. VAN ISSELT, HEIN A. KOOMANS, and JAAP A. JOLES

Department of Nephrology and Hypertension, University Hospital, and Department of Pediatric Nephrology, Wilhelmina Childrens Hospital, Utrecht, the Netherlands; and Department of Pediatric Nephrology, University Hospital, Gent, Belgium

The pathogenesis of edema in the nephrotic syndrome (NS) is classically explained by a decrease in blood volume secondary to low plasma colloid osmotic pressure (π) [1], resulting in stimulation of renal sodium reabsorption via neural [2] and endocrine [3] pathways. However, we have previously measured blood volume in a large group of adult nephrotic subjects and found values predominantly within the normal range [4]. Compensatory mechanisms such as a decrease in interstitial π appear to play a major role in the defense of circulating blood volume in the NS [5].

Children with acute relapse of the NS often show symptoms such as abdominal pain, oliguria, cold extremities, anorexia and diarrhea that are rapidly ameliorated by infusing albumin, and hence are attributed to hypovolemia [6]. On the other hand, such albumin infusions are frequently complicated by hypertension, congestive heart failure and pulmonary edema [7]. Measurements of blood volume in nephrotic children are sparse. Both low and high volumes [8–10] have been suggested in preliminary reports. However, blood volume was usually computed from albumin distribution volume and hematocrit, which is relatively insensitive because the relation between whole-body hematocrit and large-vessel hematocrit, the so-called F-cell ratio [11], is not constant between individuals. The F-cell ratio is sensitive to changes in distribution of the circulation between the microvasculature (where the hematocrit is low due to the Fahreus-Lindqvist effect) and the large vessels. Considering the large spontaneous variation found in blood volume measured by plasma volume and hematocrit in healthy adults [12] and children [13], it is questionable whether a decreased blood volume can actually be measured with this approach in nephrotic children.

Simultaneous measurements of plasma volume and red cell volume, providing more reliable assessment of whole blood volume, are not available in normal children. Recently we found that children with or without symptoms of hypovolemia due to relapse of minimal change nephrosis had blood volumes that were not different from children in remission [14]. However, it is not certain whether the latter group have blood volumes that fall within the normal range, and can serve as a reference group. The only reference values that are available in children are for blood volume calculated from plasma volume and hematocrit [13]. Also, it is unknown whether children with nephrotic syndrome are compensating for factors that are threatening blood volume by altering the distribution of blood volume between the microvasculature and the large vessels [15].

To address these questions, we measured plasma volume, as the distribution volume of iodinated-albumin, and red cell volume, and calculated the F-cell ratio in children over a large age bracket during nephrosis and in remission. Our aims were: (1) to define a reference range for plasma volume, red cell volume, blood volume and F-cell ratio in children without proteinuria between the age of 2 and 18 years; (2) to establish whether these variables fall inside or outside these defined ranges in children with nephrotic proteinuria; and (3) to elucidate whether plasma π correlates with blood volume or F-cell ratio.

Methods

Patient characteristics

Patients were classified as being nephrotic when they had a protein/creatinine ratio in their urine above 0.6 g/mmol, plasma albumin below 25 g/liter, and detectable edema. They were classified as being in remission when urinary protein/creatinine ratio was below 0.4 g/mmol, plasma albumin was above 30 g/liter, in the absence of edema. A 24-hour urine collection was not feasible in most patients, and hence the protein/creatinine ratio was used to estimate urinary protein loss [16]. In a group of children with minimal change nephropathy ($N = 34$), we studied 31 while they were in remission and 21 while they were nephrotic. In addition, we included six children with NS due to histological lesions (4 with mesangioproliferative glomerulonephritis, one with focal glomerulosclerosis and one with IgA nephropathy). Patients were selected to have normal or at most modestly disturbed renal function (serum creatinine below 100 μmol/liter). Eleven of the patients in remission were on steroid treatment. Treatment with diuretics was terminated at least one week before the start of the trial. Urine was collected prior to the start of the trial. Informed consent of all parents and guardians was obtained. The study was performed in accordance with the Declaration of Helsinki, and was accepted by the Ethical Committee of the Wilhelmina Childrens Hospital in Utrecht.

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Volume measurements

On the morning of the volume determination 5 ml venous blood was drawn for red blood cell (RBC) labeling with ^{51}Cr [17], and the left and right cephalic veins were catheterised. After at least 30 minutes of recumbency 4 ml blood was drawn to serve as a blank and for determination of plasma colloid osmotic pressure (π), total protein, and hematocrit. Then ^{131}I-HSA (human serum albumin, Amersham, UK) was injected into the laminar stream of a 10 ml pulse of saline solution via the rubber extension of a T-extension set (Abbott). This procedure was designed to avoid adhesion of the tracer to the catheter or connection set. The syringe was rinsed by flushing twice with saline, and residual radioactivity in all used material was subtracted from total counts in the syringe. Exactly 10 minutes later 4 ml blood was drawn from the contralateral arm for counting of radioactivity. Subsequently ^{51}Cr-RBC was administered by the same procedure. The radioactive doses (in msv) were calculated according to the subjects' age as follows: ^{131}I-HSA = 0.0061 × years and ^{51}Cr-RBC = 0.0073 × years, and therefore varied per subject. Potassium iodide was administered orally 12 hours prior to administration of ^{131}I-HSA. Hematocrit was determined in triplicate. Plasma π was measured with a strain-gauge oncometer. Plasma and urine protein were measured by the biuret reaction. Plasma and urine creatinine were measured by the Jaffe reaction.

Calculations

Dry weight was measured as body wt when the patients were in remission or estimated (from age, height and lowest body wt measured during treatment with diuretics and low dietary sodium prior to the study) as edema-free body wt in the patients with histological lesions, or with minimal lesions who did not go into spontaneous remission. Blood volume was calculated as red cell volume + plasma volume. Whole-body hematocrit was calculated as red cell volume/blood volume, the F-cell ratio as whole-body hematocrit/large vessel hematocrit. Body surface area was estimated using height (H) and dry body wt (DBW) with the formula of Dubois and Dubois [18]. Due to the difference in body composition between males and females [19], pubertal or older females (usually above the age of 10) should be analyzed separately. Lean body mass (LBM) was estimated from H and DBW according to the formulae:

LBM in males and prepubertal females: $0.407\ DBW + 26.7\ H - 19.2$

LBM in pubertal or older females: $0.252\ DBW + 47.3\ H - 48.3$.

These formulae have previously been derived from the empirical relation between total body water (TBW), body wt and height on the one hand and between TBW and LBM (in kg) on the other hand [12]. Elimination of TBW gives LBM (in kg) as a function of DBW (in kg) and height (in m). Regression of plasma volume, red cell volume and blood volume of the patients in remission on age, H, DBW, BSA and LBM were calculated in order to derive the most suitable index, that is, with the highest correlation coefficient in combination with an intercept that was closest to zero. This appeared to be LBM (**Results**).

Linderkamp et al [13] have measured plasma volume and hematocrit in 85 healthy children (39 ♂ and 46 ♀) between 2 and 14 years of age. They calculated blood volume using an assumed F-cell ratio of 0.91 [20, 21]. We evaluated whether the patients in remission had a similar range of values at a given age for blood volume calculated in the same manner. Subsequently, the red cell volume, plasma volume and blood volume in the nephrotic patients were normalized to LBM and compared with the normalized values as established in the subjects in remission. The F-cell ratio was also compared. Linear regression analysis of F-cell ratio on LBM was performed for the patients in remission and for blood volume and F-cell ratio on plasma π for the whole population (subjects in remission plus nephrotic subjects).

Table 1. Clinical data of patients with the nephrotic syndrome (NS) due to minimal lesions (ML), histological lesions (HL), or in remission

Diagnosis	Remission	MLNS	HLNS
Gender, male/female	22/9	13/8	4/2
Age *years*	7.9 (2.4–18.2)	7.0 (2.2–16.3)	6.0 (3.9–10.7)
Length *cm*	129 (91–176)	121 (86–161)	106 (102–130)
Dry body weight *kg DBW*	25.6 (12.0–63.5)	20.0 (11–54)	17.5 (15–27)
Body surface area m^2	0.94 (0.54–1.70)	0.79 (0.50–1.55)	0.72 (0.66–0.98)
Edema *% DBW*	—	9 (3–26)[a]	5 (4–20)[b]
Urinary protein/creatinine *g/mmol*	0.02 (0.00–0.38)	1.59 (0.61–8.4)[a]	1.30 (1.13–5.1)[b]
Plasma protein *g/liter*	67 (58–82)	43 (32–48)[a]	45 (36–51)[b]
Plasma π *mm Hg*	23.4 (18.6–29.0)	7.9 (6.0–17.0)[a]	10.9 (7.5–16.0)[b]
Plasma creatinine *μmol/liter*	46 (19–86)	45 (12–67)	50 (45–99)
Hematocrit %	37 (33–42)	39 (31–46)	30 (22–35)[b]

Data are presented as median and range and were analyzed with a Kruskall-Wallis test followed by a Mann-Whitney U-test.
[a] $P < 0.05$, remission vs. MLNS
[b] $P < 0.05$, remission vs. HLNS

Statistical analysis

Data are presented as median and range. Comparison of data from groups was performed with the Kruskall-Wallis test followed by the Mann-Whitney *U*-test. Paired data were compared with the Wilcoxon test. Linear regression and correlation coefficients were calculated by the least squares method. Regression lines were compared by analysis of covariance.

Results

The patient characteristics are presented in Table 1. There were about twice as many males in each group. The median age (and thus length, weight and body surface area) of patients with histological lesions was slightly lower than those in the other two groups. By definition edema was absent, urine protein/urine creatinine was very low and plasma protein and π were normal in patients in remission. The amount of edema in both groups of nephrotic patients showed a large variation, but the median values did not differ significantly. Plasma protein and π were reduced in both groups of nephrotic patients. Plasma creatinine was similar in all groups, and not increased. Hematocrit was somewhat reduced in patients with histological lesions.

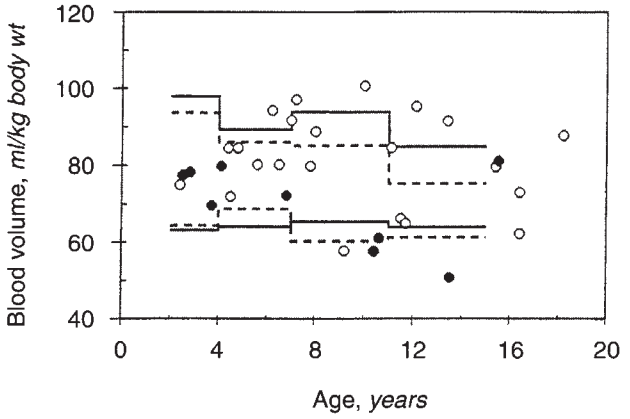

Fig. 1. *Blood volume (plasma volume/1–0.91(hematocrit)) per kg body wt in relation to age in 22 boys [○] and 9 girls [●], aged 2 to 18 years for patients in remission from minimal change nephrotic syndrome.* The continuous and dashed lines identify the normal range (twice the SD) obtained in respectively 39 boys and 46 girls aged 2 to 14 years from a study by Linderkamp et al [13] in healthy children.

Remission

Blood volume was calculated from measured plasma volume, hematocrit and an assumed F-cell ratio of 0.91 in order to compare data from the present study with those found by Linderkamp et al [13] in 85 healthy children, aged 2 to 3 years (N = 17), 4 to 6 years (N = 16), 7 to 10 years (N = 24) and 11 to 14 years (N = 28). Because Linderkamp et al [13] provide separate values for boys and girls, the normal range for both genders (twice the SD) was plotted in Figure 1. Plotting our data from the children in remission over this range reveal that these data lie within or directly above or below the normal range, without a consistent deviation in either direction. Five subjects in remission were older than 14 years, but the values in these subjects did not deviate from the range found in the younger patients. This finding supports the view that the data that we measured in subjects in remission can safely be used as a reference frame.

The mean values of plasma volume, red cell volume and blood volume (calculated as the sum of these two compartments), normalized for age, height, dry body wt (DBW), body surface area (BSA) or lean body mass (LBM) of the patients in remission are listed in Table 2. There were differences between males and females for volumes normalized by height, DBW and BSA, but this was not the case for the volumes normalized for age or LBM. All volumes were highly correlated with age, height, DBW, BSA and LBM (all $P < 0.001$), but the intercepts of the linear regression lines for blood volume normalized for age, height, DBW and BSA were much further from zero than that of the regression line normalized for LBM (Table 3). The regression lines of plasma volume, red cell volume or blood volume on LBM did not differ significantly for males and females. For these reasons, LBM was elected as the index for normalization of body fluid volumes, independent of gender.

The reference range of blood volume as a function of LBM is shown in Figure 2A. The normal range was defined as the area within twice the SD. Males and females were evenly distributed throughout the range of LBM (10 to 53 kg). The F-cell ratio showed no relation to LBM (Fig. 3) The median and range of the

Table 2. Plasma volume (PV), red cell volume (RCV) and blood volume (BV) normalized for age, height, dry body weight (DBW), body surface area (BSA) or lean body mass (LBM) as well as the F-cell ratio of the male and female patients in remission

Gender *N*	Male 22	Female 9	*P*
PV/age *ml/year*	183 (126–324)	176 (127–250)	NS (0.965)
PV/height *liter/m*	1.19 (0.83–1.89)	0.93 (0.62–1.92)	NS (0.098)
PV/DBW *ml/kg*	53.2 (38.4–66.1)	47.3 (31.9–55.3)	NS (0.068)
PV/BSA *liter/m²*	1.47 (1.20–1.89)	1.20 (0.98–1.96)	0.019
PV/LBM *ml/kg*	58.3 (44.6–67.0)	54.0 (44.5–73.8)	NS (0.572)
RCV/age *ml/year*	89 (65–128)	86 (68–98)	NS (0.514)
RCV/height *liter/m*	0.52 (0.33–0.91)	0.49 (0.25–0.65)	NS (0.177)
RCV/DBW *ml/kg*	24.6 (18.3–34.1)	20.4 (15.7–25.4)	0.007
RCV/BSA *liter/m²*	0.67 (0.50–1.05)	0.60 (0.43–0.69)	0.015
RCV/LBM *ml/kg*	26.2 (20.7–36.0)	25.0 (21.2–28.1)	NS (0.277)
BV/age *ml/year*	276 (205–451)	253 (195–348)	NS (0.828)
BV/height *liter/m*	1.73 (1.15–2.79)	1.41 (0.90–2.57)	NS (0.128)
BV/DBW *ml/kg*	78.2 (60.0–98.0)	72.5 (47.5–76.6)	0.012
BV/BSA *liter/m²*	2.16 (1.77–2.72)	1.75 (1.48–2.62)	0.013
BV/LBM *ml/kg*	84.9 (68.8–95.3)	75.2 (66.4–98.7)	NS (0.602)
F-cell ratio	0.84 (0.77–1.09)	0.81 (0.72–0.92)	NS (0.240)

Data are presented as median and (range) and were analyzed with a Mann-Whitney U-test.

Table 3. Linear regression for blood volume versus age, height, dry body weight (DBW), body surface area (BSA) or lean body mass (LBM) of the patients in remission (N = 31)

	Slope	Intercept *ml*	*r*	*P*
BV/Age *year*	218 ml/year	359	0.950	< 0.0005
BV/Height *m*	3936 ml/m	−2853	0.935	< 0.0005
BV/DBW	60.2 ml/kg	408	0.908	< 0.0005
BV/BSA	2678 ml/m²	−534	0.937	< 0.0005
BV/LBM	81.1 ml/kg	27	0.953	< 0.0005

F-cell ratio were found to be 0.83 (0.72 to 1.09; N = 31). The F-cell ratio in males and in females was 0.84 (0.77 to 1.09; N = 22) and 0.81 (0.72 to 0.92; N = 9), respectively. These values were also not significantly different.

Nephrosis

The body fluid volumes normalized for LBM and the F-cell value found in the nephrotic patients without and with histological lesions and for those in remission are shown in Table 4. The volumes for boys and girls are not presented separately because the inherent gender-related differences have been corrected for by using the appropriate normalization to LBM (see above). No differences were observed in the patients with minimal lesions in comparison to the patients in remission, irrespective of whether this was tested for the entire group or for the subgroup of 18 for which paired data were available. In the patients with histological lesions who were mildly anemic, plasma volume tended to be higher and red cell volume lower than the patients in remission, but blood volume and F-cell ratio were normal. No differences

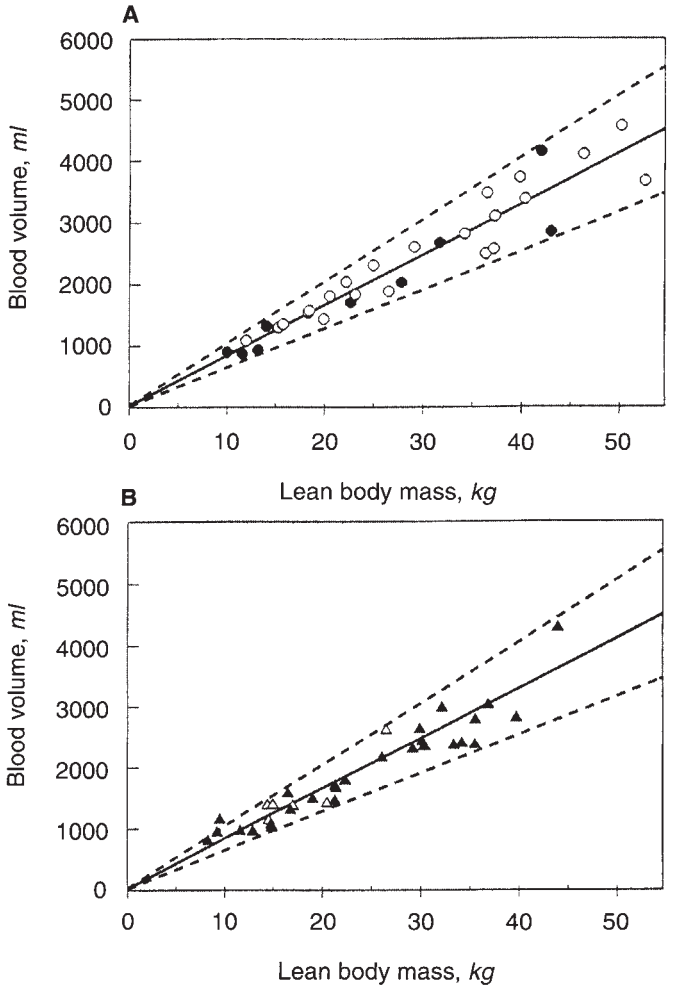

Fig. 2. A. *Blood volume (red cell volume + plasma volume) plotted against lean body mass in 22 boys [○] and 9 girls [●], aged 2 to 18 years in remission from minimal change nephrotic syndrome.* The normal range is defined as twice the SD and is identified by dashed lines. **B.** Blood volume (red cell volume + plasma volume) plotted against lean body mass in 21 patients with minimal change nephrotic syndrome (△) and 6 patients with nephrotic syndrome due to histological lesions (▲). The normal range as defined in A is indicated by dashed lines.

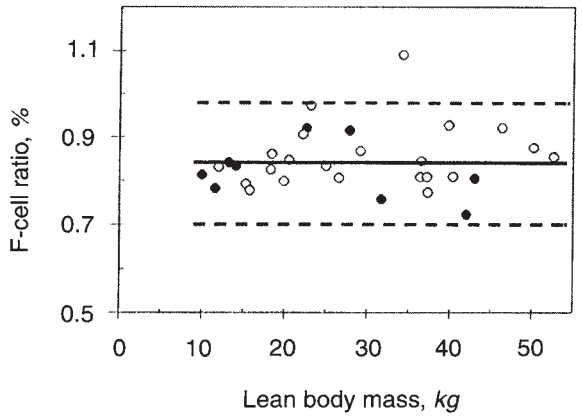

Fig. 3. *F-cell ratio (whole-body hematocrit/peripheral hematocrit) in relation to lean body mass (LBM) in 22 boys [○] and 9 girls [●], aged 2 to 18 years.* All subjects were patients in remission from minimal change nephrotic syndrome. The normal range is defined as twice the SD and is identified by dashed lines. There was no significant relation between LBM and F-cell ratio.

Table 4. Plasma volume (PV), red cell volume (RCV) and blood volume (BV) normalized for lean body mass (LBM) and the F-cell value of patients with the nephrotic syndrome (NS) due to minimal lesions (ML), histological lesions (HL), or in remission

Diagnosis	Remission	MLNS	HLNS
All patients			
N	31	21	6
PV/LBM *ml/kg*	58.3 (44.5–73.8)	55.0 (40.6–94.4)	66.2 (47.8–76.5)[a]
RCV/LBM *ml/kg*	25.4 (20.7–36.0)	25.5 (18.2–40.0)	21.5 (13.9–32.4)[b]
BV/LBM *ml/kg*	84.6 (66.4–98.7)	78.9 (67.5–123.4)	87.8 (69.9–99.6)
F-cell ratio	0.83 (0.72–1.09)	0.81 (0.59–1.07)	0.83 (0.68–1.02)
Paired data			
N	18	18	
PV/LBM *ml/kg*	58.3 (44.5–67.0)	53.9 (40.6–78.9)	
RCV/LBM *ml/kg*	24.5 (20.7–31.1)	24.6 (18.2–27.8)	
BV/LBM *ml/kg*	84.9 (66.4–95.3)	77.0 (67.5–104.0)	
F-cell ratio	0.82 (0.75–0.92)	0.82 (0.67–1.07)	

Data are presented as median and (range) and were analyzed with a Kruskall-Wallis test followed by a Mann-Whitney U-test. Paired analysis of the patients with MLNS studied both in remission and during relapse was also performed using a Wilcoxon test. [a] 0.058, [b] 0.039, HLNS vs. remission

were observed between patients with minimal or histological lesions. Blood volume in all nephrotic subjects lies within the normal range found in the control population in remission (Fig. 2B). The regression lines of blood volume on LBM for nephrotic patients and subjects in remission were not significantly different.

To observe whether a subgroup of patients with a particularly low or high plasma colloid oncotic pressure (π) were, respectively, hypovolemic or hypervolemic we plotted blood volume/LBM against π (Fig. 4) and calculated the regression of blood volume, normalized to LBM, on π. No clear differences in blood volume could be observed over a range of π that varied from 6 to 29 mm Hg, and there was no significant correlation. Similarly, the F-cell ratio did not differ over a large range of π, with the exception of four nephrotic patients with π ranging from 6.4 to 8.3 mm Hg (Fig. 5), where the F-cell ratio was below 0.7. Note, however, that 11 other patients with similarly low values for π had a normal F-cell ratio above 0.7. There was a very weak relation between F-cell ratio and π ($r = 0.251$, $P = 0.051$, $N = 58$).

Discussion

In this study a reference frame for blood volume, normalized to LBM and measured directly from plasma volume and red cell volume, was established for children between the age of 2 and 18 years that is independent of gender. Directly measured blood volume in children with the NS fell within this defined normal range. The ratio of whole-body hematocrit to large-vessel hematocrit (the F-cell ratio) was not lower in children than in adults, and

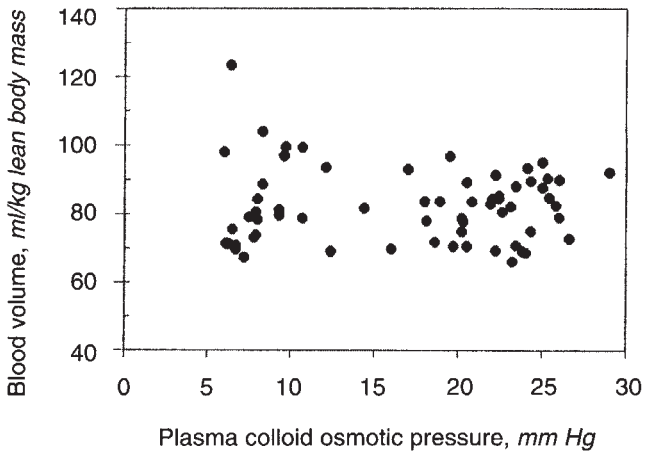

Fig. 4. *Blood volume (BV) in relation to plasma colloid osmotic pressure (π).* There was no significant relation between blood volume and π.

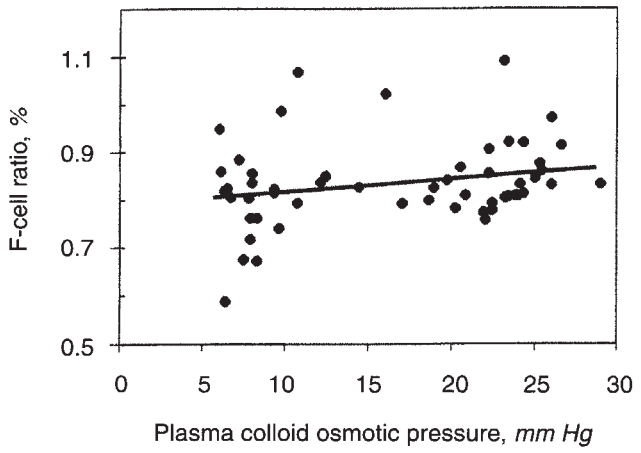

Fig. 5. *The F-cell ratio in relation to plasma colloid osmotic pressure.* There was a very weak relation between F-cell ratio and π ($r = 0.251$, $P = 0.051$).

was not disturbed in children with the NS, with the exception of a small minority of the patients with very low π.

The observation that the intercept of the relation between blood volume and LBM did not differ significantly from zero in subjects aged 2 to 18 years directly confirms a similar observation in adult subjects in our laboratory [12]. In this previous study the subjects' age varied from 19 to 72 years [12], so that we are now able to support the correction for LBM for individuals between 2 and 72 years of age. Direct comparison of plasma volume/LBM as measured in the 31 children in remission (56.6 ± 7.5 ml/kg) with plasma volume/LBM in 66 normal adult subjects (56.2 ± 6.2 ml/kg) in the previous study [12] revealed no significant difference, but red cell volume/LBM was significantly lower in the children (26.2 ± 3.9 ml/kg) than in a group of 12 adults (34.2 ± 2.4 ml/kg; $P < 0.01$) [22]. Hence, the (plasma volume + red cell volume)/LBM in the children (82.8 ± 9.1 ml/kg) was also significantly lower than the value found in the adult subjects (94.4 ± 4.5 ml/kg; $P < 0.01$) [22]. Therefore, it is advisable to use separate reference values for the children and adults for the direct comparison of blood volume because of the difference in red cell volume. The difference in hematocrit between the adults (42%) and the children (37%) is an illustration of this fact.

The frame of reference for blood volume in children established in this study provides an important tool for further study of conditions in children where an alteration in blood volume has been postulated. Expansion of blood volume is thought to play an important role in the pathogenesis of hypertension [23] and/or diabetic nephropathy [24]. In other disease states such as cardiac failure, severe liver disease with hepato-renal syndrome or bronchopulmonary dysplasia changes of blood volume may be important, but until our study, no reference data were available for children.

Hypoalbuminemia has been postulated to increase capillary permeability to albumin [25]. If this is true at albumin concentrations found *in vivo* this would lead to overestimation of plasma volume, and thus result in a lower F-cell ratio. An increased capillary permeability to albumin will lead to overestimation of plasma volume, while in fact plasma volume is maintained in the presence of increased flux of albumin through interstitium and lymphatics. However, in adult patients with the NS we were unable to find a change in F-cell ratio [22]. The transcapillary escape rate of albumin in normals ranges from 4 to 7%/hr and from 5 to 14%/hr in adult nephrotic subjects [22]. It should be noted that even if the capillary permeability to albumin was increased to the upper end of this range in nephrotic children this would have little impact on measured plasma volume, because the latter is measured as the 10-minute distribution volume of albumin, at which time at most 3% of the tracer will have been lost through the capillaries instead of the usual loss of 1% [26]. In healthy infants below the age of one year capillary permeability to albumin is known to be as high as 6%/10 minutes [20, 27]. However, the mean F-cell ratio in the healthy children above two years old in the present study (0.85 ± 0.07) was not significantly different from that found in our laboratory in healthy adults (0.86 ± 0.03 [22]). This does not exclude a slightly higher capillary permeability to proteins in children, but if present it is apparently accompanied by a weaker Fahreus-Lindqvist effect, so that there is no net effect on F-cell ratio.

Reports of direct measurement of blood volume in nephrotic children are sparse [8–10], and two of these are preliminary [8, 10]. As in our study, most of the patients were males. This gender-related difference in incidence of the NS in children is well known [28], albeit unexplained. Masuda et al [8] found hypovolemia in edematous children when compared to remission, whereas Li, Wang and Lu [10] found the reverse. Ormantaeva found hypovolemia only in young children with NS, but the reference population was not defined [9]. None of these reports provide absolute values for the measured blood volume. In the present study blood volume in the nephrotic children was not different from that found in the control population. This confirms previous observations from our department in adults with the nephrotic syndrome [22], but is in direct contrast to what has been reported by others in large series of adult patients [29, 30]. Part of the confusion may be due to the fact that blood volume measurements by this group have been related to wet body wt [29, 30]. Clearly, patients who have accumulated large amounts of edema in the compliant interstitial space (a threefold increase in extracellular fluid volume has been recorded [31]) will be categorized as being hypovolemic with this approach.

Redistribution of extracellular protein from the intravascular to

the extravascular space probably supports blood volume homeostasis in patients with a stabilized hypoproteinemia [5, 32]. It is well known that an acute decrease in plasma π, induced by plasma pheresis, will induce hypovolemia [33]. However, 20 hours later normovolemia is present without restoration of normoproteinemia [34]. In patients with an established NS the decrease in plasma π is matched by a decrease in interstitial fluid π [32, 35, 36], so that the transcapillary colloid osmotic gradient (plasma π–interstitial fluid π) is maintained. These findings, as well as the observation that when patients with edema come into remission a negative sodium balance can be maintained for several days despite severe hypoproteinemia [37], have lead to the postulate that a primary defect in renal sodium handling is responsible for sodium retention in these patients [4, 26, 38]. This is supported by direct observations in different models of experimental nephrosis [39–42].

A situation can be conceived in which proteinuria is so protracted and severe that interstitial protein stores become depleted and the transcapillary gradient of π is seriously compromised, resulting in edema via the classical "underfill" pathway. The experimental work performed in dogs indicated that this occurs below a plasma π of about 8 mm Hg [34], a value termed the oncotic threshold for edema formation. There were 15 NS patients with a value of π below 8.4 mm Hg (6.0 to 8.3). However, even in this range no relation was present between plasma π and blood volume (Fig. 5). One possibility is that interstitial π is appropriately decreased in these patients. But this would imply an interstitial π close to zero, which is unlikely because of the continuous flux of plasma proteins through the capillary membrane to the interstitial space. The other possibility is that non-albumin protein, that is retained to a greater extent in the vascular space, is contributing importantly to plasma π, as has previously been found in adult patients with NS [43]. The F-cell ratio was decreased in a minority of these patients (3 of 15 = 20%) with the most severely decreased plasma π. It is conceivable that in these three patients there was some increase in capillary permeability causing overestimation of plasma volume and thus decreasing the F-cell ratio. The corollary of this argument is that in this subgroup some degree of hypovolemia was present. However, when effective circulating blood volume is threatened, peripheral vasoconstriction mobilizes fluid reserves. This mechanism decreases the circulation to the small vessels and thus, if anything, tends to increase the F-cell ratio, as has been observed in dogs after bleeding 30% of blood volume [44]. Thus whether these children were truly hypovolemic is not certain.

In summary, normal reference frames for blood volume, measured as the sum of red cell volume and plasma volume and adequately normalized for LBM, and F-cell ratio, the ratio of whole-body and large-vessel hematocrit, were defined in children. Blood volume was not found to be subnormal in a large group of pediatric patients with a marked decrease in plasma π due to the NS. A slight decrease in F-cell ratio was observed in a minority of patients with plasma π below 8.3 mm Hg. This may indicate a decrease in blood volume in this subcategory that would have remained undetected by measurements of plasma volume and hematocrit only. Thus, when using a rigorously defined normal range, we could find practically no evidence of hypovolemia in nephrotic children.

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Reprint requests to Dr. J.A. Joles, Department of Nephrology and Hypertension (FO3.226), Utrecht University Hospital, P.O. Box 85500, 3508 GA Utrecht, The Netherlands.

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