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ORIGINAL ARTICLE

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Changes of renal flow volume in the hemolytic-uremic syndrome – color Doppler sonographic investigations

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Abstract Varying degrees of vascular occlusion can be found in the hemolytic-uremic syndrome (HUS). This is the rationale for Doppler sonographic investigations of renal blood flow in children with HUS. In 1989 a first report suggested a close relationship between normalization of the resistive index (RI) of renal blood flow with the restitution of urine flow in affected children. Later reports did not confirm these initial findings. The aim of this paper is to describe renal volume perfusion quantitatively in children with HUS. The renal arteries in 35 patients with HUS (1 month to 15 years) were investigated at the onset of HUS by color Doppler ultrasonography. Flow volume measurements were carried out in the 1st week and in the 2nd to 4th week after onset of the disease. These data were compared with measurements from a healthy pediatric population of 69 children. Statistically significant changes in renal perfusion occur in the flow volume of the kidneys. The flow volume dropped to 32% (34%) in the 1st week of the disease compared with the normal population and recovered in 2–4 weeks to 117% (65%) of the normal flow volume (left kidney in parentheses). The new technique of volumetric perfusion measurement overcomes some drawbacks of the traditional RI, which may have led to some confusion in the past.

Keywords Hemolytic-uremic syndrome · Renal perfusion · Volumetric flow measurement · Color Doppler ultrasonography · Nutcracker syndrome · Body surface area-related flow measurement

Introduction

The hemolytic-uremic syndrome (HUS) is the most-frequent cause of acute renal replacement therapy in children. Initially a thrombotic process triggered by verotoxin or other damaging insults obstructs the renal vasculature. Renal function is often seriously depressed and anuria, edema, and hypertension may occur. This life-threatening situation is usually treated with dialysis. Renal damage is temporary, but subclinical sequelae often remain. In 15%–81% of all patients full renal function is never restored [1]. Some patients remain on maintenance dialysis and require transplantation. It is not clear at the onset of the disease which patients are at high risk of remaining in renal insufficiency. Some authors consider the type of HUS a prognostic factor. D^+ HUS (with diarrhea) is regarded as prognostically more favorable than D^- HUS (without diarrhea) [1]. Others have not confirmed this finding [2].

Sonography is useful in evaluating renal function. In B-mode sonograms, bright parenchyma, substantial swelling of the kidneys, poor visualization of the central complex, and an empty urinary bladder characterize the typical picture in HUS. Functional aspects cannot be estimated sufficiently with the conventional B-mode sonograms.

Histological investigations from the first description of the HUS [3], which were confirmed and extended by the French groups of Habib and Gervais, clearly demonstrated varying degrees of vascular occlusion in the course of the disease [4, 5, 6, 7]. Hence, it is no surprise that Doppler sonography shows alteration of blood flow in these patients. The first to demonstrate this was Patriquin et al. in 1989 [8]. They described an elevation of resistive index (RI) in the acute phase of HUS and suggested its use for prediction of the onset of diuresis.

However, conflicting results were reported later [9, 10, 11, 12]. Our own studies demonstrated repeatedly that even with adjacent intrarenal vessels the spectral analysis and the RI varied substantially.

In a healthy pediatric population we demonstrated previously the use of quantitative volume perfusion measurements [13]. This new technique of measurement of the volume flow may provide insights into damage of the renal vasculature in HUS.

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The aim of this study was to describe the alteration of flow volume in the initial phase of HUS and to define whether volume flow measurement could reflect alteration of renal perfusion more reliably than the RI.

Materials and methods

Patients

Thirty-five children aged 1 month to 15 years with HUS were investigated with color Doppler ultrasonography (CDUS) from the onset of the disease to the end of the 4th week. Twenty-two patients recovered without sequelae, 5 developed chronic renal insufficiency, and 8 had end-stage renal insufficiency. No deaths occurred.

All patients fulfilled the diagnostic criteria for HUS:

1. Thrombocytopenia less than 100 megaparticles/l
2. Hemolytic anemia [in all patients the anemia was hemolytic and microangiopathic: the blood smear showed irregular erythrocytes (helmet cells, fragmentocytes) and the children had an elevated bilirubin, whereas haptoglobin and/or hemopexin were below normal]
3. Acute renal insufficiency (significant rise of creatinine and urea) and oliguria or anuria

The renal arteries were examined by CDUS and volume flow was determined. These measurements were compared with those of 69 healthy children aged 4 weeks to 17 years. In 2 cases the right renal artery was not sufficiently visible to carry out a reliable renal volume flow calculation.

Sonographic investigation

Sonographic investigation was carried out in the prone position in transverse and longitudinal sections of the kidneys. The children were not sedated but were distracted by their parents to prevent excessive restlessness and crying.

Body surface area (BSA) was calculated according to Haycock et al. (1978): $BSA=0.024265*L^{0.3964}*W^{0.5378}$ (L: body height; W: body weight [14].

The renal artery was evaluated for a linear segment near the hilus. If multiple renal arteries existed, each vessel was measured separately and the overall volume flow was calculated by addition.

The width of the blood column was directly measured from the color duplex scan. Multiple measurements were carried out (2–8) and the mean value of the width (d) was applied. The mean velocity [time averaged velocity (TAV)] was determined from the spectral analysis of the Doppler curve, and from these raw data the body surface area-related renal volume perfusion (BSARVP) was calculated as follows:

$BSARVP=TAV*d2/4*\pi/BSA$

For more details see also Scholbach [13].

Equipment

All investigations were carried out with the Ultramark 9 Color Doppler System (Advanced Technology Laboratories, Bothell, Washington, USA). This device is equipped with cineloop and video recording. A 3.5-MHz curved array, 2.5-MHz sector or 5-MHz linear array transducer were also used.

Statistical analysis

The Mann-Whitney U Wilcoxon rank sum W test was used to determine significant differences between healthy children and patients with HUS. A P value less than 0.05 was regarded as significant.

Results

During the acute phase of HUS a significant reduction of the BSARVP was observed (Fig. 1, Fig. 2, Table 1). In the 1st week renal perfusion was reduced. Later a restitu-

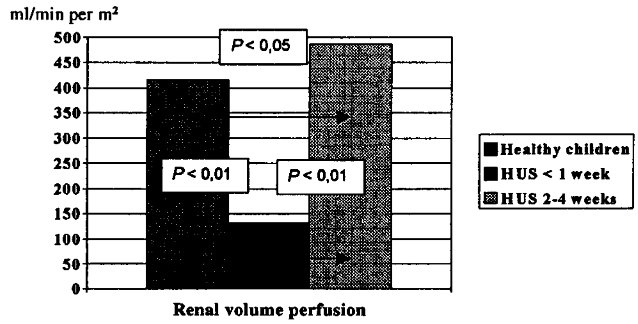

Fig. 1 Volume perfusion of the right kidney in the acute phase of hemolytic-uremic syndrome (HUS) (1st and 2nd to 4th week after onset of the disease) – comparison with healthy children

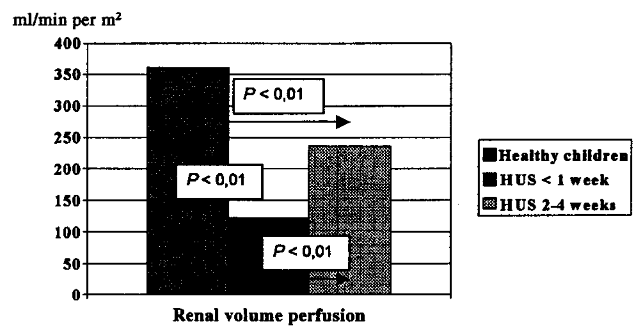

Fig. 2 Volume perfusion of the left kidney in the acute phase of HUS (1st and 2nd to 4th week after onset of the disease) – comparison with healthy children

Table 1 Body surface area-related renal volume perfusion (BSARVP) in both kidneys in the initial phase of hemolytic-uremic syndrome (HUS) compared with a group of healthy children

		BSARVP	
		Left kidney	Right kidney
Healthy children	Mean	361	416
	SD	182	190
	n	69	67
HUS (1 week)	Mean	122	132
	SD	104	94
	n	31	30
HUS (2–4 weeks)	Mean	236	486
	SD	142	1,143
	n	35	34

tion of perfusion began, and was more pronounced in the right than in the left kidney.

Our investigation (details not given here) showed that children with diarrhea had a significantly shorter stay in hospital ($P<0.05$) and a significantly lower probability ($P<0.01$) of developing chronic or terminal renal insufficiency. There were no significant differences between children with and without diarrhea with respect to duration of anuria, oliguria, thrombocytopenia, severity of cerebral symptoms (none, convulsions, permanent cerebral damage), or development of arterial hypertension.

Discussion

Our results indicate a pronounced depression of the renal volume perfusion in the 1st week after the onset of HUS and the beginning of its resolution in the 2nd to 4th week. This is consistent with previous observations of an elevated RI in the acute phase [8]. The latter study recommended using the elevation of the peripheral resistance in the renal vasculature to predict the restitution of sufficient diuresis in an affected individual. Other authors have reported conflicting observations in patients with HUS [9, 10, 11, 12]. Some found no value in evaluating renal function with the RI. Our investigations (results not published) indicated that the disease selectively affected some parts of the renal vascular tree. Some branches of the renal vascular tree (interlobar arteries) were more obstructed than others. This agreed with the histological description of kidney biopsy specimens in HUS [15, 16]. This selective, branch-specific, focal destruction of the vasculature might be the reason for the inconclusive results reported by various researchers.

With the use of CDUS it is easier to find flow signals from tiny vessels inside the kidneys. Some investigators have traced their Doppler spectra from interlobar arteries. If an interlobar artery has a greatly diminished flow only faint signals will be detected. If the vessel is completely obstructed flow vanishes and no Doppler signal can be found. In this way a bias develops, with signals from better-perfused areas being over-represented and vessels without flow being excluded from evaluation.

The traditional way to estimate the quality of flow is the RI, which reflects the so-called vascular resistance. An increase in the resistance is thought to reflect worsening perfusion. While this may be true in many situations, this assumption will fail in situations where the driving force (i.e., arterial pressure) is strong enough to force more blood into the renal vasculature than the actual capacity of the vasculature allows. The backpressure from the vasculature – the resistance – will rise, and the flow volume may increase despite an increasing RI. Our own investigations (results not shown) demonstrated counter-directed changes of the systolic and diastolic velocity with increase of renal perfusion. RI alone may therefore be unreliable for the estimation of the real perfusion of an organ. RI is a semiquantitative parameter based upon only two velocity values (maximum systolic and end-diastolic) of the whole heart cycle. One reason for using RI in the past was the inability of early Doppler equipment to demonstrate the course of smaller vessels. Exact velocity measurements were not possible in many vessels because the angle between the transducer and the direction of the vessel could not be determined if the vessel could not be outlined with the conventional B-mode technique. The only way to obtain an impression of the quality – not quantity – of perfusion was to use a ratio of the maximum (systolic) and minimum (end-diastolic) velocity. Currently exact velocity measurements during the whole heart cycle are possible. The angle and the width of vessels, even when not observable in conventional sonograms, can be reliably measured with CDUS. This forms the basis of flow volume measurements in this paper.

Renal function depends on adequate blood perfusion. It is therefore useful to measure the real renal volume flow instead of vascular resistances (RI). This can be achieved solely by the investigation of the renal main artery (or arteries). The vessel diameter is measured, and the cross-sectional area is calculated and multiplied by the mean flow velocity. Thereby the volume of blood flowing through the kidney can be calculated.

We demonstrated in previous investigations that the BSARVP can be measured reliably in healthy children [13] by CDUS. A significant correlation between the ^{123}I-hippurate clearance (r=0.70, P=0.00) and the BSA-related flow volume in children was demonstrated. No differences between girls and boys in the plasma flow of kidneys have been demonstrated by scintigraphy [17, 18, 19]. Moreover, there are no differences between male and female children with regard to their packed cell volume [20]. Serum creatinine values differ between sexes only in adolescents and adults. We speculate that in both of these groups differences of muscle mass and body size are the reasons.

The BSARVP is equal in all age groups throughout childhood. This allows comparison of renal perfusion between all patients, regardless of their age or weight. It seems advantageous to use a BSA-related flow volume.

The renal volume flow is substantially depressed at the beginning of the disease, and there are no significant differences between the left and the right side. Flow volume is restored by the end of the 4th week. The amelioration of perfusion is more pronounced in the right than in the left kidney (Fig. 1, Fig. 2). The earlier restitution of blood flow in the right kidney may be due to the variable compression of the left renal vein in the so-called arterial nutcracker. This is a clamp formed by the superior mesenteric artery and the aorta, which compresses the left renal vein in some patients. This compression results in an elevated venous backpressure, which influences the renal arterial perfusion [21, 22]. Children with the nutcracker phenomenon of the left renal vein have a lower volume flow of the left kidney and a higher RI compared with the right kidney [23]. Differences in the variability of flow parameters within both kidneys have been described earlier in a healthy population, when the nutcracker phenomenon was not ruled out [24]. In this investigation of severely ill children, no attempt was made to rule out children with the

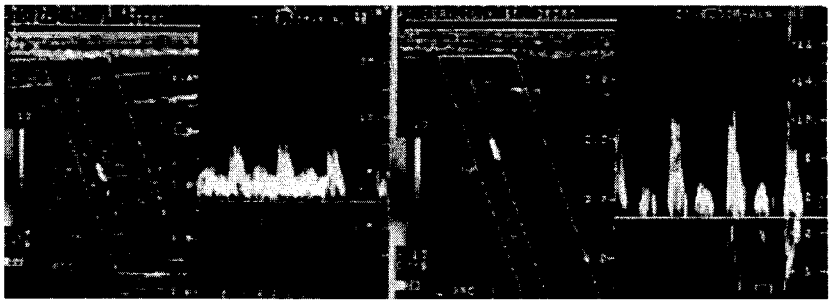

Fig. 3 Strikingly different flow patterns in one kidney of a child with HUS. The measurements were made in adjacent interlobar arteries during the same investigation

nutcracker phenomenon. The assumption that this alters the renal perfusion is reasonable, according to observations in 2,116 children reported by the author [21].

According to our flow measurements the acute phase of HUS is finished after the 1st month. The volume flow is then similar to a healthy population (Table 1).

The volume flow measurements constitute a great advantage over traditional RI measurements. Our observations (Fig. 3) demonstrated that even in adjacent interlobar arteries striking differences of the RI may exist. This is the Doppler sonographic correlate of the varying and focal histological occlusion of intrarenal vessels, as described by Argyle et al. [15] and Tinaztepe et al. [16]. Quite different degrees and patterns of vascular damage may occur in a single kidney. This explains why the RI from some parenchymal arteries (interlobar arteries) cannot be a reliable means of estimating the alteration of renal perfusion or even predict renal function. Figure 3 illustrates the unreliability of the RI as the only parameter of blood flow. Therefore, the use of CDUS to measure the real blood flow volume represents noteworthy progress in the evaluation of children with HUS.

The value of volume flow measurements in the prediction of renal function and the discrepant development of the components of the RI (systolic, diastolic, mean flow velocity) are subjects of current investigation.

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