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Intrarenal Resistance Index for the Assessment of Early Renal Function Impairment in Patients with Liver Cirrhosis

M. Götzberger, C. Kaiser, N. Landauer, C. Dieterle, W. Heldwein, U. Schiemann

Medizinische Klinik - Campus Innenstadt, Klinikum der Universität München, Munich, Germany

Abstract

Background: Renovascular vasoconstriction in patients with hepatorenal syndrome can be quantified by the renal arterial resistance index (RI). We investigated the value of RI measurement in detection of renal function impairment in patients with different stages of chronic liver disease.

Methods: Subjects were divided into 4 groups containing 21 patients with liver cirrhosis and ascites, 25 patients with liver cirrhosis without ascites, 35 patients with fatty liver disease and 78 control subjects. All patients underwent abdominal ultrasound examination with renal RI measurement and correlation with laboratory results for renal function.

Results: RI was significantly higher in ascitic patients compared to non-ascitic patients (0.74 vs. 0.67, $p < 0.01$) and in non-ascitic patients with liver cirrhosis than in control subjects (0.67 vs. 0.62, $p < 0.01$). 48 % (19/40) of patients with liver cirrhosis and normal serum creatinine concentration showed elevated RI levels. There were no significant differences in RI levels between patients with fatty liver disease and controls (0.63 vs. 0.62).

Conclusions: Intrarenal RI measurement is a predictor of renal vasoconstriction and serves to detect early renal function impairment in cirrhotic patients. The diagnosis of elevated RI may be taken into account in the clinical management of these patients.

Key words: Liver cirrhosis, hepatorenal syndrome, Duplex Doppler ultrasonography, intrarenal resistance index, fatty liver disease

Background

Renal dysfunction often develops in patients with liver cirrhosis. The impairment of kidney function is caused by severe renal arterial vasoconstriction due to complex changes in systemic hemodynamics [1, 2]. Hepatorenal syndrome (HRS) is the most serious complication of renal dysfunction in patients with end-stage liver cirrhosis and is associated with an extremely short survival time [3, 4]. Renal arterial vasoconstriction may persist for weeks, even months before an increase of blood urea nitrogen or serum creatinine values can be discovered [5]. Therefore better methods to diagnose this early stage of renal disease are needed.

Duplex Doppler ultrasonography of the kidneys is an easy and non-invasive method to assess blood flow and arterial vascular resistance as a parameter for vasoconstriction [6-8]. The arterial resistance index is the most widely used parameter to estimate the arteriolar vascular resistance. It is regularly used for screening of transplant rejection or to diagnose renal artery stenosis [9]. A positive correlation has been described between intrarenal RI and plasma renin activity as well as plasma aldosteron concentration [10]. The activation of the renin-angiotensin-aldosterone system plays an important role in the pathogenesis of hepatorenal syndrome [1].

To define the prognostic value of RI measurement for renal function impairment in patients with different stages of chronic liver disease more precisely, we analysed intrarenal arterial resistance index in patients with liver cirrhosis compared to RI levels in patients with fatty liver disease and a control group of healthy subjects.

Patients and Methods

Patients

146 patients with chronic liver disease underwent sonographic examination with RI evaluation. 65 subjects were excluded due to manifest hepatorenal syndrome, gastrointestinal bleeding, spontaneous bacterial peritonitis or other acute infections with potentially or overt cardiovascular instability. Also excluded were subjects with concomitant insulin dependent diabetes mellitus, suspected or overt malignant diseases, patients with nephropathies and with pathomorphological findings in ultrasound like decreased kidney size, reduction of parenchymal width and significant parenchymal hyperechogenicity.

81 patients and 78 control subjects were finally enrolled in the study. Subjects were divided into four groups.

- group 1: 21 patients with liver cirrhosis and ascites
- group 2: 25 patients with liver cirrhosis without ascites
- group 3: 35 patients with fatty liver disease
- group 4: 78 control subjects without any liver or kidney disease

The diagnosis of liver cirrhosis was based upon typical clinical and sonographical findings (irregular homogeneity of the liver, liver surface nodularity, reduced portal flow velocity) [11] as well as characteristic laboratory results (elevated transaminases and γ-

GT, abnormal liver function tests, such as spontaneously decreased PI and hypoalbuminemia). Additionally, 16 of the 46 patients with liver cirrhosis had undergone computed tomography or magnetic resonance tomography of the liver. In 4 cases with unclear findings, cirrhosis was verified by liver biopsy. The diagnosis of fatty liver disease was based on typical sonographic parameters (hepatomegaly, increased echogenicity with continuously decreased dorsal echogenicity). The aetiology of cirrhosis in group 1 and 2 was alcoholic in 31 of the 46 patients (67%) and posthepatitic in 11 (24%). 4 patients (9%) had histories of other chronic liver diseases like M. Wilson, primary biliary cirrhosis (PBC) and autoimmune hepatitis.

Duplex Doppler ultrasound is a routine, non-invasive method. All patients were orally informed about the procedure of the study, which is conforming to the declaration of Helsinki. Abdominal ultrasound scan and laboratory tests were part of the routine diagnostic work-up for all patients attending our department in case of liver cirrhosis, fatty liver disease or other gastrointestinal disorders.

Methods

All patients underwent an abdominal ultrasound examination of the liver, the portal vein and both kidneys including Duplex Doppler evaluation of the renal arteries using a 3.5-MHz convex transducer (Siemens Sonoline Elegra, Erlangen, Germany). All examinations were performed by two experienced investigators (M.G., C.K.). The patients were asked to fast at least 4 h before examination to reduce masking by gas. Doppler signals were taken from segmental arteries near the renal hilum (seg) and arcuate arteries of the cortex (arc) in both kidneys. Colour doppler ultrasound was used to help to identify the arteries. A train of at least three similar, sequential time-velocity waveforms of Doppler signals was obtained at each point of measurement during suspended respiration (Fig. 1a and b). The RI was calculated with the formula RI = (peak systolic velocity – end diastolic velocity)/ peak systolic velocity. Patients were excluded if it was not possible to measure the RI in two different places in each kidney due to massive ascites or masking by gas.

Laboratory results for liver and renal function (bilirubine, albumin, prothrombin time, transaminases, cholinesterase, creatinine, urea nitrogen, electrolytes) as well as a set of clinical parameters including arterial blood pressure, heart rate, age, gender, signs of hepatic encephalopathy and finally the Child-Pugh score were obtained of all patients.

Statistical Analysis

Results were expressed as means ± standard deviation. Differences among groups were evaluated by Kruskal and Wallis non-parametric test. The 5% probability level was regarded as significant. Linear correlation was performed for the data of RI and age in the control group 4 and age was considered as a co-variate for the analysis calculating the differences in RI levels between the groups.

Results

Table 1 shows the main clinical characteristics and laboratory parameters of the different study groups. In group 3 and 4 laboratory results showed normal renal function for all patients. Group 1 and 2 together included in total six patients with serum creatinine elevated up to 2.5 mg/dl. Group 1 patients presented with lower blood pressure and more severe laboratory signs of hepatic insufficiency than group 2 patients. Accordingly, group 1 patients showed a Child-Pugh score C in 57% and a child B score in 43%, whereas patients in group 2 revealed mostly Child-Pugh score A (64%).

All patients showed normal kidney size and normal parenchymal structure in ultrasound examination. In all groups single RI measurement did not significantly differ neither for an individual subject nor for a single kidney. There were no significant differences in RI values comparing left and right kidney as well as parenchymal regions (seg or arc) within a subject (Table 2). Consecutively, we calculated a mean RI value for each subject based on the 4 measurements.

In the control group, linear regression analyses showed a positive correlation between the arterial resistance index and the age ($r = 0.32$, $p<0.01$). Therefore, age was considered as an independent variable on the RI value in evaluating differences in the RI values within the different groups. The mean RI level was significantly higher in cirrhotic patients (RI = 0.70) than in control subjects (RI = 0.62, $p<0.01$). Among cirrhotic patients, the six patients with elevated serum creatinine had a mean RI value of 0.77. RI was significantly higher in those patients than in cirrhotic patients with normal serum creatinine ($n = 40$, RI = 0.69) ($p<0.05$).

Additionally, the RI was significantly higher in nonascitic patients with liver cirrhosis than in control subjects (0.67 vs. 0.62, $p<0.01$) and in ascitic patients compared to nonascitic patients (0.74 vs. 0.67, $p<0.01$) (Fig. 2). There were no significant differences in RI levels between patients with fatty liver disease and the control group (0.63 vs. 0.62, n.s.).

81% of the patients in group 1 and 28% in group 2 showed elevated RI levels >0.70, but only 3% of the subjects in group 3 and 4.

Discussion

Mortality in patients with advanced liver cirrhosis is very high. The identification of predictors for prognosis and mortality remains part of researches. Among the existing prognostic models, the Child-Pugh score is most widely used, although the score has some weaknesses, such as dependence upon observer interpretation [12]. Additional parameters in predicting the prognosis of liver cirrhosis are needed.

Patients with liver cirrhosis regularly develop renal failure due to intrarenal vasoconstriction. Manifest HRS is associated with a very poor outcome lacking effective therapeutic strategies [3]. Doppler ultrasound measurement of the RI is a useful index to quantify renovascular resistance in cirrhotic patients before HRS develops.

Previous data show that RI values decrease from renal hilum to the cortex [13]. RI values measured in the

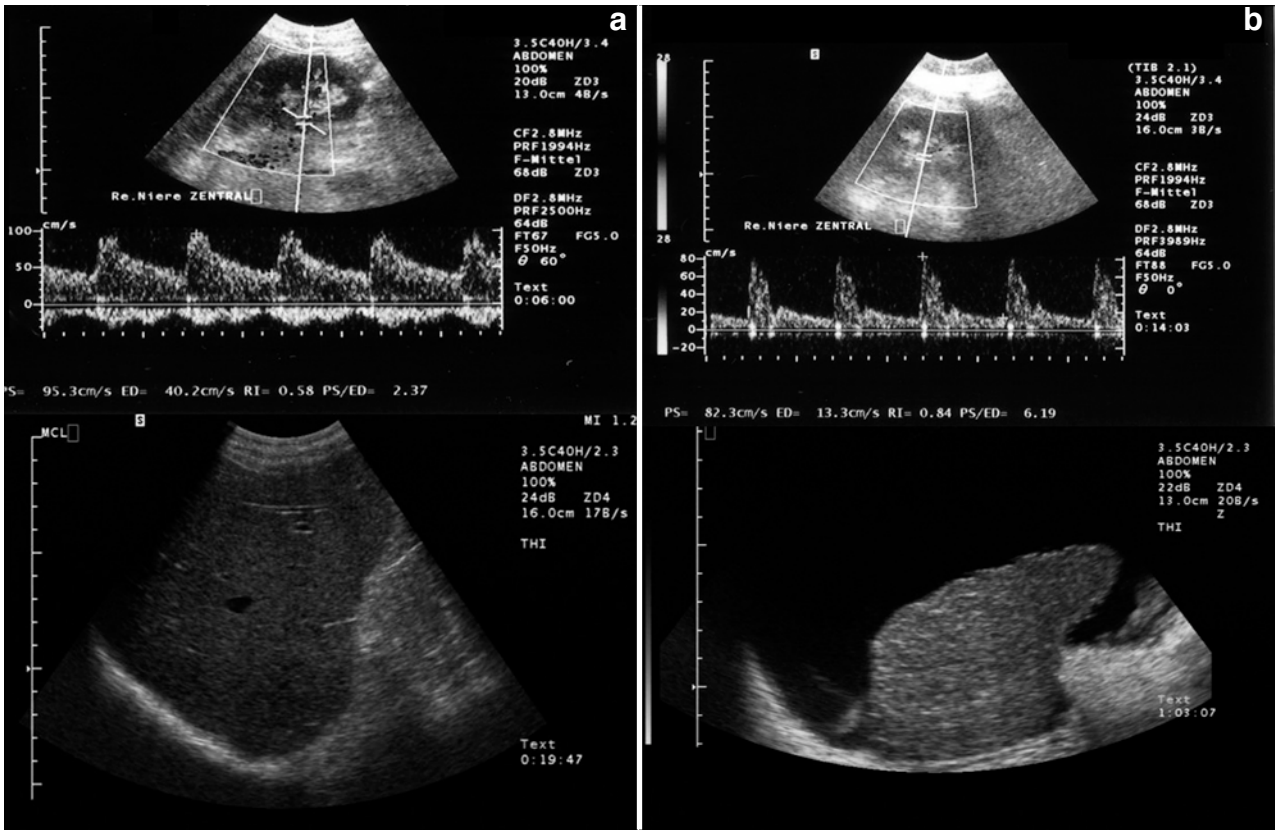

Fig. 1a and b. Doppler ultrasonography of intrarenal arteries is used for RI measurement. Time-velocity waveform is registered to calculate the RI. *Fig. 1a* shows normal RI = 0.58 (above) in a control subject with normal liver scan (below). *Fig. 1b* shows elevated RI = 0.84 (above) in a patient with liver cirrhosis and ascites (below).

interlobar-arcuate arteries are expected to show the most consistent results [13]. Our results confirmed a slight decrease between these two points of measurement (seg-arc), but the difference was not significant. No significant difference between left and right kidney was found in our groups either. Concerning variability in RI measurement, Keogan and coworkers recommended to average a number of at least three measurements in one kidney to obtain a single representative value [14]. Therefore one representative value averaged from three measurements in one region appears to be sufficient to assess the RI in a patient. Even if it is not possible to measure the RI in four different points for each subject due to poor conditions it is possible to reach a reliable result for the RI value. In addition, among experienced investigators trained for this method, interobserver variability is very low [15].

On the basis of previous studies intrarenal RI of 0.70 was considered as a threshold value being indicative of increased renal vasoconstriction [10, 16, 17]. RI levels in 5 of our 6 patients with liver cirrhosis and elevated creatinine were >0.70 with an average RI of 0.77. The correlation between increased RI and azotemia seems to confirm the role of vasoconstriction in the pathogenesis of cirrhotic kidney disease [18]. However, intrarenal arterial RI values were already significantly increased in the group of nonascitic cirrhotic patients and even higher in ascitic patients than in control subjects. Thus, RI measurement seems to identify renal vasoconstriction at an earlier time than elevated serum creatinine values. In the literature, three other studies can be found that evaluated RI measurement in ascitic and nonascitic patients with cirrhosis. These studies also show higher RI levels in cirrhotic patients with ascites than in nonascitic subjects [7, 18, 19]. In contrast to our data, these studies were done in a smaller group of healthy controls and no correlation with age was taken into account, although RI levels significantly increases with age [14]. In addition, we also investigated RI levels in patients with fatty liver disease. Nonalcoholic fatty liver disease is a common cause of elevated liver enzymes [20]. Although it carries a risk for progressive liver disease and cirrhosis, fatty liver disease alone generally has a benign course [20, 21]. No differences in RI measurement could be found between this group and the control subjects confirming that this stage of liver disease seems not to be associated with renal impairment.

Elevated RI values are more commonly seen in patients with advanced stage of liver cirrhosis, but can be regularly found in patients with clinical stages Child A or B. Therefore, the renal RI can play an additional role in evaluating the severity and prognosis of the disease. Platt and coworkers performed a long term follow up of 180 patients with cirrhosis without azotemia showing that, despite similar Child-Pugh scores, the outcome for HRS and renal dysfunction was significantly worse in patients with initially elevated RI values [5]. Within the group of 76 patients with RI $\geq$ 0.70, 55% developed kidney dysfunction and

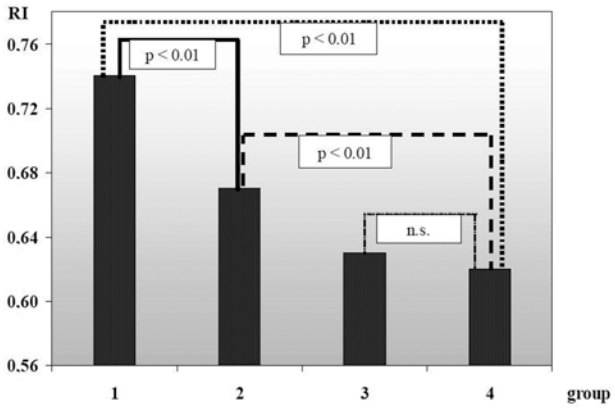

Fig. 2. Significant higher RI values can be found in ascitic patients with cirrhosis (group 1) as well as in nonascitic patients (group 2) compared with control group 4. Ascitic patients showed significantly higher RI than nonascitic patients. Patients with fatty liver disease (group 3) presented with normal RI values.

Table 1. Clinical and laboratory characteristics in each group of patients.

group		*1* n = 21	*2* n = 25	*3* n = 35	*4* n =78
age (yr)		56.9 ± 14.1	56.5 ± 11.8	49.3 ± 10.1	46.2 ± 13.1
gender	female	8	7	7	32
	male	13	18	28	46
arterial pressure	systolic	106 ± 13	117 ± 14	129 ± 9	123 ± 12
(mmHg)	diastolic	69 ± 9	76 ± 10	79 ± 5	78 ± 7
heart rate (/min)		80 ± 9	81 ± 6	80 ± 6	77 ± 8
Child-Pugh	A (%)	0	64	-	-
score	B (%)	43	36	-	-
	C (%)	57	0	-	-
Serum creatinine (mg/dl) (normal range 0.5 - 1.2 mg/dl)		1.0 ± 0.4	0.8 ± 0.3	0.9 ± 0.2	0.8 ± 0.2
GFR (ml/min)		77.8 ± 28.0	100.2 ± 30.7	104.3 ± 26.5	103.0 ± 23.6
Blood urea nitrogen (mg/dl) (normal range 9 - 23 mg/dl)		18 ± 17	13 ± 6	11 ± 4	13 ± 6
Serum sodium (mmol/l)		136± 5	141 ± 4	140 ± 4	141 ± 3
Cholinesterase (U/l)		3.0 ± 1.2	6.3 ± 3.3	8.2 ± 2.5	7.8 ± 1.9
Serum bilirubin (mg/dl)		3.3 ± 2.7	1.8 ± 1.9	0.7 ± 0.4	0.7 ± 0.6
Serum albumin (g/dl)		2.9 ± 0.6	3.8 ± 0.7	4.5 ± 0.6	4.4 ± 0.4
Prothrombin time (%)		58 ± 13	80 ± 13	98 ± 6	97 ± 6
hepatic encephalopathy	non	12	24	-	-
	stage I / II	9	1	-	-
	stage III / IV	0	0	-	-

Group 1 represents patients with liver cirrhosis and ascites, group 2 non-ascitic patients with liver cirrhosis, group 3 patients with fatty liver disease, group 4 control subjects. Data are expressed as means ± standard deviation. GFR = Glomerular filtration rate. GFR was calculated by the MDRD formula.

Table 2. Intrarenal RI values of the four different patient groups in the left and the right kidney at segmental and arcuate arteries, respectively.

group	*1* n = 21	*2* n = 25	*3* n = 35	*4* n = 78
RI right seg	0.74 ± 0.06	0.68 ± 0.06	0.63 ± 0.05	0.62 ± 0.05
RI right arc	0.73 ± 0.07	0.67 ± 0.06	0.62 ± 0.05	0.62 ± 0.04
RI left seg	0.75 ± 0.05	0.68 ± 0.06	0.62 ± 0.05	0.62 ± 0.05
RI left arc	0.73 ± 0.05	0.67 ± 0.06	0.63 ± 0.05	0.61 ± 0.05
RI mean value	**0.74**	**0.67**	**0.63**	**0.62**
patients with RI > 0.70	17 (81 %)	7 (28 %)	1 (3 %)	2 (3 %)

Data are expressed as means ± standard deviation.
Seg = Segmental arteries, Arc = Arcuate arteries.

even 26% hepatorenal syndrome, whereas only 6% (6/104) of the subjects with normal RI <0.70 developed kidney dysfunction at the end of follow up ($p<0.01$) [5]. In 48% (19/40) of our patients with liver cirrhosis and normal creatinine elevated RI >0.70 could be found, including nonascitis subjects and patients with Child-Pugh classification B. Intrarenal RI seems to be a helpful predictor to identify a subgroup of patients with higher risk of developing kidney failure or HRS. Follow-up studies are required to quantify the prognostic value of elevated RI. A long term follow-up of our cirrhotic patients is already pending. First results show a tendency for higher frequency of renal dysfunction in the group of patients with previously elevated RI. A 67-year-old man with serum creatinine of 1.0 mg/dl and elevated RI = 0.73 died after 9 months due to hepatorenal syndrome, a 65-year-old women with serum creatinine = 0.9 mg/dl and RI = 0.77 developed after 15 months elevated serum creatinine = 2.4 mg/dl, whereas another 47-year-old man (serum creatinine = 0.6 mg/dl) with normal RI = 0.59 remained stable after 15 months of follow-up with RI = 0.62 and serum creatinine of 0.8 mg/dl.

We conclude that the evaluation of intrarenal RI appears to be an easy to perform, non-invasive method providing only with low costs for the assessment of early renal impairment in patients with liver cirrhosis due to increased vasoconstriction. Patients with renal vasoconstriction are at higher risk of developing manifest renal failure [22, 23]. Therefore, elevated RI values may be taken into account in clinical management of these patients, e.g. in the use of nephrotoxic agents. At least a strict regular control of clinical and laboratory results should be performed.

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Address for correspondence:
Manuela Götzberger, M.D.
Klinikum der Universität München
Medizinische Klinik – Campus Innenstadt
Ziemssenstr. 1
80336 München
Germany
Tel.: +49-89-5160-2111
Fax: +49-89-5160-2105
E-mail: manuela.goetzberger@med.uni-muenchen.de