Abstract

Aims: The aim of this study was to calculate the normal values of renal functional reserve in healthy individuals measuring the resistive index and pulsatility index using Doppler ultrasonography. Material and methods: Forty healthy volunteer adults were included in the study. Their basal resistive index and pulsatility index values were measured and after oral protein load at 30th, 75th and 120th minutes, resistive index and pulsatility index measurements were repeated. The maximum changes in resistive index and pulsatility index from baseline were calculated in each subject which represented the renal functional reserve. Results: The mean values of resistive index and pulsatility index decreased significantly starting with 30 minutes and consecutively at 75 and 120 minutes (for all p<0.05). The highest decrease compared to baseline values was recorded at 75 minutes and renal functional reserve values were calculated as 22.2% for resistive index and 25.4% for pulsatility index. Conclusion: Renal functional reserve can be calculated through Doppler resistive index and pulsatility index measures. We consider that it may be helpful to know normal values of renal functional reserve in healthy subjects. Keywords: protein intake, penal functional reserve, Doppler ultrasound, resistive index, pulsatility index

Introduction

Doppler investigations permit noninvasive monitoring of the perfusion of various organs. Recent developments have caused the widespread use of Doppler ultrasonography (US) in the assessment of various kidney diseases [1-3]. Doppler examination has been used in the diagnosis of renal artery stenosis, renal vein thrombosis, complications secondary to biopsy, assessment of renal inflammation, obstructive collecting system dilatation and in the evaluation of renal vascular resistance in various renal parenchymal diseases such as diabetic nephropathy, systemic lupus erythematosus, autosomal-dominant polycystic kidney disease, hepatorenal syndrome, hemolytic uremic syndrome, or interstitial nephritis [1,2,4-11].

The resistive index (RI) and pulsatility index (PI) measurements provide information about arterial impedance [1]. The RI value in the spectrum is the ratio of the difference between the peak systolic velocity (PSV) and the end diastolic velocity (EDV) divided by PSV value: RI= (PSV-EDV)/PSV . PI value is found by dividing the difference between peak systolic velocity (PSV) on Doppler spectrum and end diastolic velocity (EDV) with mean velocity (MV): PI=(PSV-EDV)/MV . The vessel diameters and the angle of the Doppler beam do not impact on both indices. In a healthy adult population, RI of 0.70 and PI of 1.20 are used as the threshold values for increased renal vascular resistance [1]. The RI and PI are indirect but sensitive indices of the degree of vasoconstriction. In addition, both indices are reflecting the resistance of the tissues against the blood flow in the vascular bed induced by changes such as cellular infiltration, interstitial edema, increased hydrostatic pressure and colloid osmotic pressure. The other factors that may influence RI and PI are the reduction of the vascular bed (such as glomerular capillary damage, destruction), the intrin-
sic reduction of vascular diameter of causes different from vasospasm (such as stenosis, endothelial edema), and the venous outflow obstruction. For each index, the lower the value, the lower the resistance, thus, the flow increases. Several studies demonstrated that increased RI and PI can be found in various parenchymal kidney diseases such as hemolytic-uremic syndrome, interstitial nephritis, diabetic nephropathy, autosomal-dominant polycystic diseases [1,2,4,6,12].

On the other hand, new methods to reveal the impairment of the renal function in early stages are being investigated. Glomerular filtration rate (GFR) is usually accepted as the best overall index of kidney function in health and disease. Normal GFR varies according to age, sex, and body size. In young adults it is approximately 120-130ml/min/1.73 m² and declines with age. However, baseline GFR does not necessarily correspond to the extent of functioning renal mass. A test of stimulation to reach maximal GFR might be helpful to define the real situation of the subject in terms of renal function. It is known that the normal kidney has the ability to increase the GFR and renal blood flow in response to certain stimuli such as oral protein load, amino acid or dopamine infusion [13-15].

The concept of a baseline and maximal GFR in humans has been defined by the so called “renal functional reserve” (RFR). RFR is an index of the capability of the kidney to increase its function by vasodilatation of the arterioles and activate the dormant nephrons [13-15]. In 1984, Bosh et al [16] introduce this term, defining RFR as the capacity of a kidney to increase its GFR according to the incremental of metabolic demands or in response to an acute oral protein load. The reduction or the absence of RFR could imply that the residual nephrons are already in a state of permanent glomerular hyperfiltration. There is no constant value or nomogram for RFR but it has been shown to vary between 10% and 70% of the baseline GFR in healthy subjects [15,17]. Likewise, there is no constant relationship between the GFR and changes in RFR; the RFR may be decreased before any change occurs in the GFR [14,15]. As progressive renal impairment occurs, the RFR reaches zero value at some point of the decrease of the level of baseline GFR.

The mechanisms of RFR that cause an increase in both GFR and renal blood flow following protein loading are not well known, but the hormones involved include glucagon, glomerulopressin, prostaglandins, and angiotensin-2 [13]. Changes in the tubular handling of sodium may also play a role. On the other hand, glomerular hyperfiltration occurring as a secondary effect of a high protein diet has been reported to accelerate the deterioration of renal functions [13,18]. Therefore, the decrease or absence of RFR may be an early indicator of impaired renal function.

Pulsed Doppler US is a widely used technique which allows rapid, repeated, direct, noninvasive measurement of renal blood flow. Each recording takes only a few minutes after identification of the interlobar artery, and the results are instantly available. The RI and PI measurements can be used in the assessment of RFR [15,19]. The objective of this study was to determine normal RFR values, using the RI and PI measurements in healthy adults and to discuss what benefits this parameter may provide in clinical monitoring.

**Material and methods**

Forty healthy volunteer adults (21 male, 19 female, median age 41.5 years [range, 27-56], with no renal disease, diabetes, or hypertension) were recruited from subjects submitted for routine abdominal US between September 2014 and February 2015. All subjects signed an informed consent before inclusion and the study protocol was approved by the local Ethics Committee. Routine biochemical and hemogram tests have been performed in every case before US examinations. Median body mass index (BMI) was calculated 23 kg/m² (range, 19-27). Obese patients whose US evaluation could not be performed optimally were excluded from the study. Renal function abnormalities (serum creatinine level >1.2 mg/dL, creatinine clearance <90 ml/min, and proteinuria) and US renal abnormality (such as cysts, atrophy, nephrolithiasis) were also excluded.

In order to minimize effects by personal factors, all measurements were made by a single radiologist experienced in Doppler US. Investigations were performed with a General Electric Logiq 9 machine using a 3.5 MHz convex probe, in the supine position via translumbar approach applied to both kidneys. The flow spectra were obtained from the interlobar arteries in both kid-
neys so that the highest Doppler frequency shift could be achieved. The software on the US computer memory was used to measure RI and PI values (fig 1).

Renal RI and PI were measured from pulse Doppler waveforms obtained from interlobar arteries in three different regions from the upper, middle and lower third of the kidney. From each recording, the RI and PI were measured only when at least three consecutive Doppler waveforms with similar appearance were noted. The RI and PI for each kidney were calculated as an average of three RI and PI values. Also, a mean RI and PI were calculated by averaging mean RI and PI of the right and left kidney. No significant differences were found in the RI and PI between the right and left kidney for each subject.

Doppler US examination was started at 09.00 a.m., after fasting overnight. Fasting baseline RI and PI were measured. The volunteers then ate a 250g steak containing approximately 70g protein, without added salt, over a maximum of 30 minutes. They also drank 500 ml water. After oral protein loading, the RI and PI indices were measured again in the 30th, 75th and 120th minutes and the minimum RI and PI values obtained. The maximum changes in RI and PI from baseline were calculated in each subject representing the RFR (as a percentage change). The baseline RI and PI values of each subject before the steak meal worked as the control values.

As the data were normally distributed, the student’s t test for paired data was used to calculate the significance of differences between the baseline and minimum RI and PI. The results given as mean (standard deviation) and p<0.05 were considered significant.

Results

Doppler US was successfully performed in all subjects enrolled. The RI and PI measurements and RFR calculations were recorded. The results on baseline (fasting), after loading oral protein, 30th, 75th and 120th minutes mean RI and PI measures and RFR values are in table I. As can be seen in the table, after the protein loading starting from the 30th minute, continuing with the 75th and 120th minutes, the RI and PI values were significantly decreased from the baselines values (for all p<0.05). The lowest values of both indices were obtained at the 75th minute. It was observed that the values from the 120th minute showed a tendency to return to baseline values (fig 2). For this reason, RFR values were calculated with baseline values compared with 75th minutes values and found as 22.2% for RI and 25.4% for PI.

Age and sex did not affect RI and PI or RFR. There was no correlation between the BMIs and the values of RI, PI, and RFR. Likewise, no correlation was found between the serum creatinine levels and creatinine clearance and both indices and RFR values (for all p>0.05).

Discussions

Color duplex Doppler US enables visualization of blood flow in renal and intrarenal arteries and provides noninvasive evaluation of renal vascular resistance by measuring pulsatility and resistive indices. In addition, RI and PI could be useful predictors of renal function deterioration, and both indices were significantly correlated with organ damage including glomerular sclerosis, interstitial fibrosis/tubular atrophy, interstitial infiltration, and arteriolosclerosis [12,20,21]. However, there are only a few studies which have investigated RFR in patients with renal deterioration using Doppler US [15,19].

Until about the fourth decade, renal blood flow is maintained at approximately 600 mL/min. It then drops by approximately 10% every decade due to the activation of the sympathetic nervous system, the renin-angiotension-aldosterone system, and vasopressin secretion [22,23]. A series of studies have indicated that the aging kidney is characterized by a decline in renal function...
and by a susceptibility to renal diseases and nephrotoxic injuries [22-24]. However, it is not clear whether the observed changes have hemodynamic, structural or both origins [24]. Esposito et al [24] divided healthy participants into young (age range 25-37 years), middle-aged (44-74 years) and elderly (81-96 years) and concluded that renal function is preserved with aging in healthy subjects at the expense of a complete reduction of RFR. RFR may be wasted to compensate for the increased number of sclerotic glomeruli [24]. Kawai et al [12] investigated the correlation between RI and the influence of aging on renal hemodynamic status and they demonstrated that renal vascular resistance and intra-renal arteriosclerosis had a greater impact on renal function in older (age >75) than younger (age <75) subjects, reflecting the possible mechanisms of renal function reduction due to aging. In our study, we evaluated RFR using RI and PI in healthy adults (age range 27-56) and there was no significant correlation between Doppler indices and age, sex, BMI, serum creatinine, and creatinine clearance.

Kalantarinia et al [25] utilized contrast-enhanced ultrasound (CEUS) to monitor the expected increase in renal blood flow following a high protein meal in healthy adults. CEUS is a suitable imaging technique for the assessment of renal blood flow, but the disadvantage of this technique is to inject intravenously ultrasound-contrast agents (gas-filled microbubbles) to enhance the ultrasound image. We utilized RI and PI measurements to calculate RFR. Renal Doppler US is a fast, noninvasive, and practical imaging technique. RI and PI measurements can be made on the same flow spectrum, and on the 75th minute after oral protein loading, RFR can easily be calculated using both indices.

Sharkey et al had used only PI on the investigations of RFR in chronic obstructive pulmonary disease (COPD) cases [15]. Chen et al [19] had used the RI before and after oral protein loading to determine the RFR in patient with COPD. We used RI and PI indices in combination to calculate RFR and aimed to use both indices as a confirmation of each other. The results are compatible with one another, and these two indices provide similar values to each other (22.2% for RI and 25.4% for PI).

In this study, we demonstrated that RFR can be calculated by Doppler RI and PI measurements. Furthermore, for the first time the relationship between fasting and after protein meal was assessed using both indices in normal individuals. Our results show that intrarenal arterial resistance decreased with protein loading and the lowest values in both indices were obtained at the 75th minute after a protein meal in healthy subjects. This decreasing of RI and PI can be defined as “Doppler RFR” and its normal value should be approximately 20% or more in healthy subjects. Reduced or lost ratio refers to a pathological condition. This description in Doppler investigations could be useful in clinical practice for the determination of renal abnormalities.

The limitation of this study is that normal Doppler RFR values are not calculated separated by age groups. In addition, more comprehensive Doppler US comparison studies are needed to assess the correlation between the creatinine clearance or GFR values and the Doppler RFR ratio. Furthermore, more studies with larger numbers of participants are required to confirm these findings, measuring hemodynamic indices.

In conclusion, in the early diagnosis of renal functional impairment as a result of various diseases, RFR assessment can be performed by Doppler ultrasonography which is a noninvasive method. Doppler RFR values of normal individuals are considered useful to be known.

References

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