Age-Related and Vasomotor Stimuli-Induced Changes in Renal Vascular Resistance Detected by Doppler Ultrasound

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Indirect measurement of renal vascular resistance by duplex Doppler waveform analysis was evaluated in relation to aging and some pathophysiological conditions. Baseline renal resistive index (RRI) (peak systolic frequency shift - lowest diastolic frequency shift/peak systolic frequency shift) was measured in healthy controls aged 20 to 65 years by analyzing the blood flow velocity waveform of interlobar arteries. RRI changes induced by sympathetic activation (cold pressor test and handgrip test) or by fluid load were evaluated. Both repeatability and reproducibility were very good, as the intra- and interoperator variations were all less than their reproducibility coefficients. RRI showed a significant increase with aging (ANOVA P < .001), particularly evident in subjects older than 50 years. Both the cold pressor test and handgrip test induced in all the subjects (n = 16) a significant increase in RRI (P < .001), from 0.59 ± 0.04 to 0.69 ± 0.04 (12 ± 6%) for the cold pressor test and from 0.57 ± 0.03 to 0.66 ± 0.03 (15 ± 2%) for the handgrip test. In eight subjects intravenous fluid load (0.25 mL/kg/min of 0.9% NaCl for 120 min) caused a significant decrease in RRI (P < .001), from 0.62 ± 0.02 to 0.53 ± 0.01 (17 ± 2%), which was inversely related to mean blood pressure rise (r = −0.71, P < .001). These data show that pulsed wave Doppler analysis is an accurate method for an indirect evaluation of changes in renal vascular resistance induced by common vasomotor stimuli. Am J Hypertens 1996; 9:461-466

KEY WORDS: Renal resistive index, reproducibility, aging, vasomotor stimuli.

In the last few years, duplex Doppler waveform analysis has been accepted as a reliable noninvasive method for the indirect evaluation of renal vascular resistance.1-3 Its application to human investigation has found growing interest once it has been shown that renal resistive index (RRI) was linearly related to changes in renal blood flow.1,2,4 Thus the measurement of the RRI has been extensively used in the follow-up of renal transplants,5-8 for a noninvasive diagnosis and grading of renal artery stenosis,1,2,9-11 and to differentiate interstitial from glomerular disease.12 Recently RRI evaluation has also been proposed for the evaluation of changes in renal vascular resistance in systemic diseases such as hypertension13 and complicated liver cirrhosis,14 which are known to induce an increase in renal vascular tone. Moreover the Doppler ultrasound technique was proved to be particularly useful for monitoring RRI variations in critically ill patients.15 However, until now data have been lacking regarding the capacity of duplex Doppler waveform analysis in evaluating physiological changes in renal vascular resistance, such as those due to aging or to sympathetic stimuli.16

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In order for Doppler ultrasound to be applied in clinical conditions, however, good reproducibility and repeatability are mandatory. The reproducibility of RI measurements has been evaluated only in a group of patients with renal allograft but not in a large group of normal subjects. In the present study the RI reproducibility and repeatability have been assessed in two groups of normal subjects of different age. Both reproducibility and repeatability were good, as the differences between the measurements obtained by the same or by different operators were always less than their corresponding reproducibility index independent of the age of the subjects examined.

Another important finding from the present study concerns the consistent differences of the RRI in relation to age. With aging the RRI progressively increased, and the differences were significant between each 2 decades. Therefore, the clinical evaluation of RRI measurement in different patients should always take into account the age of the patients. The increase in the RRI observed in older, apparently healthy, subjects most likely reflects both progressive physiological reduction in arterial vascular compliance and age-modifies the relation between systolic and diastolic frequency shift, the changes of this ratio allow the investigation of the modifications of distal vascular resistance. This method has been applied to the study of peripheral vascular resistance of the cerebral, mesenteric, and femoral vascular beds. Moreover, the RRI obtained by duplex Doppler waveform analysis has been demonstrated to be linearly related to renal blood flow, measured by radionuclide scintigraphy.

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FIGURE 2. Interobserver variability (reproducibility). Upper: First measurement of RRI by M.B. v first measurement by S.S with line of equality superimposed. Lower: Differences v means of the corresponding first measurements taken by the two operators. Interobserver variation was always less than the reproducibility coefficient (2 SD). *RRI = Renal resistive index.

FIGURE 3. RRI age-related modifications. In 100 subjects aged 20 to 85 years RRI increased significantly with aging (ANOVA P < .001), and in subjects over 50 years the difference was significant also in adjacent groups (P < .05). *RRI = Renal resistive index.
related modifications in renal architecture. Renal blood flow evaluated by radionuclide scintigraphy was proved to be well maintained at about 350 ml/min until approximately the 4th decade, and then to decline by about 10% each decade, with a real progressive reduction in blood flow per unit of kidney mass.

Sympathetic activation is known to reduce renal blood flow. Pulsed wave Doppler analysis of interlobar arteries was found to be able to detect changes in renal vascular resistance induced by both the cold pressor and handgrip tests; following these tests, a significant increase in the RRI was observed in all the subjects. The percentual RRI increase induced by the application of adrenergic stimuli was higher than that of the mean arterial pressure. This result is not surprising, as the RRI directly reflects changes in the renal vascular tree, whereas blood pressure is an indirect expression of modifications in systemic arterial resistance.

Cold pressor and handgrip tests seem to induce a more marked vasoconstriction in the renal vascular tree than in the systemic arteries. This finding is consistent with the observation that sympathetic stimuli can induce a different level of activation in various target organs.

The decrease in the RRI observed after blood volume expansion by intravenous fluid load is further evidence for the RRI as a reliable index of renal vascular tone. It is well known that the increase in blood volume is accompanied by a decrease in renal vascular resistance and an increase in diuresis. In conclusion, measurement of the RRI by pulsed wave Doppler analysis is a repeatable and reproducible, even if indirect, method for the detection of renal vascular resistance. This methodology is able to detect age-related modifications of the RRI or modifications induced by physiological vasoconstricting (cold pressor and handgrip tests) or vasodilating (acute volume expansion) stimuli.

REFERENCES


This study aimed to investigate the ability of duplex Doppler waveform analysis to detect changes in renal vascular resistance caused by aging and by application of stimuli that are able to induce either vasoconstriction or vasodilatation of renal arteries, such as sympathic activation or intravenous fluid load, respectively.19

METHODS

Population and Study Design The study population consisted of healthy controls who underwent duplex sonography of the native kidneys, after giving informed consent. A total of 100 subjects (50 men and 50 women, aged 20 to 85 years) were studied under basal conditions. No subject was affected by cardiovascular disease, hypertension, diabetes mellitus, or renal disease. All therapy was discontinued at least 2 weeks before the study. Alcohol, caffeine, and cigarettes were all prohibited 48 h prior to the beginning of the study. All subjects were examined in supine position in the morning after 12 h overnight fasting and after 30 min of acclimatization at constant room temperature (22°C).

To evaluate possible changes of RRI induced by aging, the subjects were divided into six age groups (<30, 31 to 40, 41 to 50, 51 to 60, 61 to 70, and >70 years). In addition, RRI variations were evaluated in 16 controls, aged 20 to 40 years, under stimuli known to induce either vasoconstriction of renal arteries, such as the isometric handgrip and cold pressor tests, or vasodilatation, such as intravenous fluid load. During the tests heart rate was continuously monitored by an electrocardiographic lead II. Arterial blood pressure was measured by using the standard sphygmomanometer technique, and mean arterial pressure was then calculated according to the formula: diastolic pressure + (systolic pressure − diastolic pressure) / 3.

Isometric handgrip test was performed in eight subjects (five males and three females, aged 27 to 33 years) employing a handgrip dynamometer.18 The maximal individual force was estimated before starting the test. After a resting period of 30 min in supine position each subject supported 30% of his or her maximal force by handgrip for 4 min. Heart rate, blood pressure, and RRI were recorded under basal conditions, at the 1st, 2nd, 3rd and 4th minute of the test and at the 2nd, 5th and 10th minute of recovery.

Cold pressor test was performed in the same condition subjects by ice-water immersion of one hand for 5 min.19 Heart rate, blood pressure, and RRI were recorded under basal conditions, at the 1st, 2nd, 3rd, 4th, and 5th min of the test and at the 2nd, 5th, and 10th min of recovery.

Intravenous volume load was performed in another group of 8 subjects (6 men, 2 women, aged 26 to 34 years) by administering isotonic saline (0.9% NaCl; 0.25 mL/kg/min) for 2 h 30 min after insertion of 2 intravenous lines into superficial forearm veins.20 Heart rate, blood pressure, and RRI were recorded under basal conditions, every 30 min during infusion, and 30 and 60 min after the end of the test. Blood samples for the determination of hematocrit were collected at the beginning, at the end, and 60 min after the end of the test.

Equipment, Doppler Examination Technique and Signal Analysis A Toshiba Sonolayer SSA-270 (Toshiba, Tokyo, Japan) with color Doppler sonography and a 3.75 MHz sector electronic probe was used. The RRI determinations were obtained by two experienced sonographers (M.B. and S.S.). Both kidneys were scanned in supine position, by anterior and lateral approach. For the application of vasodilating and vasoconstrictive stimuli, only one kidney was chosen for RRI determination in relation to best explorability. The sample volume of the Doppler beam was placed on interlobar arteries visualized by color and the blood flow velocity waveform was recorded. The Doppler signal was analyzed by an internal software program, and the RRI was calculated using the following formula:21

| (peak systolic frequency-shift − lowest diastolic frequency-shift) / peak systolic frequency-shift |

The RRI is a dimensionless Doppler flow index that allows one to avoid the correction for the angulation of the Doppler beam against the direction of blood flow. The RRI of at least 2 and up to 5 equivalent waveforms from the same renal region were averaged to obtain the mean value of the resistive index. For the evaluation of age-related RRI variations, mean resistive indexes from more than one renal region were averaged. The operators were not only unaware of each other's measurements, but were also blinded to the on-line display of their own calculated indices by masking off the relevant section of the Toshiba display screen. A hard copy printout of each record was obtained for subsequent statistical analysis. For heart rate more than 80 beats/min, the corresponding RRI was adjusted according to the formula proposed by Mostbeck.22 Intra- and interobserver variations were evaluated in 10 subjects (5 men and 5 women) aged 30 to 40 years and in 10 subjects (5 men and 5 women) aged 60 to 70 years.

Statistical Analysis Results are expressed as mean ± standard deviation. For the evaluation of RRI measurements repeatability and reproducibility, analysis of the results was performed using the method described by Bland and Altman.23 The data were first plotted and a line of equality was drawn to provide a visual assessment of the degree of agreement. The differences between the measurements were then plotted against the mean of the differences, and the mean and standard deviation of differences were calculated. The reproducibility coefficient, as defined by the British Standards Institution, is twice the standard deviation.24 Age de-
pendent RRI variations were evaluated by ANOVA. The effects of stimuli were evaluated by Student's t test for paired samples. P < .05 were considered statistically significant.

RESULTS

Intracobserver variation (repeatability) was evaluated for each operator (M.B. and S.S.) comparing and plotting against each other two sets of RRI measurements obtained in both 10 young and 10 old subjects. There was a good agreement between the two sets of both operators as shown by the line of equality superimposed (Figure 1). Moreover, for each observer the intraoperator variation was always less than the reproducibility coefficient (0.08 for M.B. and 0.06 for S.S.).

Analogous in order to analyze the interoperator variability (reproducibility), the first measurements taken by both observers were plotted against each other and the line of equality was superimposed (Figure 2). The differences between the measurements were all less than their reproducibility coefficient (0.08), both for young and old subjects.

RRI showed a significant increase with aging (ANOVA P < .001) (Figure 3). Although there was a wide overlapping of RRI between subsequent decades, RRI values observed in 20 years-distant age-groups were always significantly different (P < .05). In subjects older than 50 years, RRI also differed significantly between adjacent groups (P < .05). No significant difference between RRI values of males and females in each group was observed.

Both handgrip and cold pressor tests induced in all subjects an effective sympathetic activation; in fact, mean arterial pressure significantly increased during the application of both stimuli (P < .05), whereas heart rate rose significantly only during handgrip (P < .05). During handgrip, RRI significantly increased in all subjects from 0.57 ± 0.03 to 0.66 ± 0.03 (12 ± 6%), reaching the maximal values at the 4th min of the test (P < .001). The RRI returned to baseline at the 10th min of recovery (Figure 4). Similarly, the cold pressor test induced in all the subjects a significant increase of RRI (P < .001). The cold-induced rise of RRI was from 0.59 ± 0.04 to 0.69 ± 0.04 (15 ± 2%). In three subjects, the highest value was observed at the 3rd, and in five subjects, at the 5th min of the test. Ten min after the end of cold application the RRI values returned back to baseline (Figure 4).

Intravenous fluid load caused in all the subjects an effective plasmatic volume expansion; in fact hematocrit values showed an average reduction of 14%, from 41.4 ± 4.8 to 35.7 ± 4.8 (P < .01), and mean arterial pressure values rose slightly from 95 ± 7.2 to 105 ± 5.7, whereas heart rate was unmodified. During fluid load RRI significantly decreased in all the subjects, from 0.62 ± 0.02 to 0.53 ± 0.01 (17 ± 2%) (P < .001). The minimum value was reached in four subjects after 90 min of infusion, and in the other four subjects at the end of infusion. A total of 60 min after the end of infusion mean arterial pressure, hematocrit values, and RRI returned back to baseline (Figure 4). Mean arterial pressure changes were inversely related to RRI modifi-
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