Color duplex Doppler sonography in the diagnosis of atherosclerotic or fibromuscular dysplastic renal artery stenosis

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Key words: Hypertension; Renal artery stenosis; Doppler studies

Purpose. To determine whether the sensitivity and specificity of extrarenal and intrarenal duplex Doppler parameters are influenced by the atherosclerotic or fibrodysplastic nature of the renovascular disease.
Materials and Methods. One hundred fifty-five hypertensive patients were enrolled in this prospective study: 93 had essential hypertension, 39 had atherosclerotic renal artery stenosis (ARAS), and 23 had fibrodysplastic renal artery stenosis (FDRAS). The following extra- and intrarenal indexes were measured during color Doppler and Doppler spectral analysis examinations for diagnosis of renal artery stenosis: peak systolic velocity (V), renal-aortic ratio (R), time of systolic acceleration (T), systolic acceleration (A), pulsatility index (PI), and resistance index (RI). The cut-off value for each index was determined by receiver operating characteristic (ROC) curve analysis.
Results. Renal arteriography demonstrated 75 stenotic renal arteries: 46 (61%) due to atherosclerosis and 29 (39%) due to fibromuscular dysplasia. The R showed high sensitivity (93%) and specificity (96%) in detecting atherosclerotic lesions. The same index revealed high specificity (97%) but low sensitivity (72%) for detecting fibromuscular dysplasia. Among intrarenal indexes T was the most sensitive: in 9/46 arteries with atherosclerotic stenosis there was no increase in the T, while 40/218 normal arteries showed T values above normal.
Conclusion. Color Doppler sonography is more reliable for detecting atherosclerotic stenosis than fibrodysplasia of renal arteries. The R is the most useful index for diagnosing ARAS.

L'ecografia color/duplex Doppler nella diagnosi di stenosi renale di tipo aterosclerotico o di tipo fibrodisplastico

Parole chiave: Ipertensione; Stenosi delle arterie renali; Eco Doppler

Scopo. Stabilire se i risultati in termini di sensibilità e specificità degli indici velocimetrici extra- ed intrarenali duplex Doppler sono influenzati dal tipo di malattia renovascolare: aterosclerotica o fibrodisplastica.
Materiali e Metodi. Sono stati arruolati per questo studio prospettico 155 patienti ipertesi: 93 pazienti con ipertensione essenziale, 39 con stenosi delle arterie renali di tipo aterosclerotico (ARAS) e 23 pazienti con stenosi delle arterie renali di tipo fibrodisplastico (FDRAS).
Per la diagnosi di stenosi renale, nel corso dell'esame eco color/duplex Doppler, sono stati ottenuti i seguenti indici velocimetrici, extra- ed intrarenali: picco della velocità sistolica (V), rapporto renale-aortico (R), tempo di accelerazione sistolica (T), accelerazione sistolica (A), indice di pulsatilità (PI) ed Indice di Resistenza (RI). Il valore di riferimento di normalità per ciascun indice velocimetrico è stato determinato mediante l'analisi statistica delle curve ROC (receiver operating characteristic curves).
Risultati. L'arteriografia renale ha evidenziato 75 arterie renali stenotiche: 46 (61%) causate dall'aterosclerosi e 29 (39%) causate dalla fibrodisplasia muscolare. L'indice velocimetrico R ha mostrato una alta sensibilità (93%) ed una alta specificità (96%) nella diagnosi di stenosi renale di tipo aterosclerotico. Lo stesso indice ha evidenziato una alta specificità (97%) ma una bassa sensibilità (72%) nella diagnosi di stenosi renale di tipo fibrodisplastico. Tra gli indici velocimetrici intrarenali il tempo di accelerazione sistolica T è stato il più sensibile nella diagnosi di stenosi renale di tipo aterosclerotico: in 9/46 arterie renali con stenosi aterosclerotica l'indice T non è risultato aumentato, mentre in 40/218 arterie renali normali l'indice T è risultato aumentato rispetto al valore normale.
Conclusione. L'ecografia color/duplex Doppler è più utile per la diagnosi non invasiva di stenosi renale di tipo aterosclerotico che per la diagnosi non invasiva di stenosi renale di tipo fibrodisplastico. Il rapporto renale-aortico (R) è l'indice velocimetrico più utile per la diagnosi di stenosi renale di tipo aterosclerotico (ARAS).

Introduction

Although color Doppler and Doppler spectral analysis modalities are widely used for non-invasive assessment of renal artery stenosis, their clinical usefulness is still debated (1-15).

The results that have been reported vary significantly depending on the equipment used in the study, inter- and intraobserver variability and site of pulsed Doppler sampling (16,17), the specific extra- and intra renal

Doppler spectral analysis indexes considered (18-23), the normal reference values for these indexes, the prevalence of renovascular disease, and the degree of renal artery stenosis (24,25). Moreover, it is unclear whether the nature of the stenosis, i.e., atherosclerotic versus fibrodysplastic lesions, can also influence the validity of this technique.
The aim of our study was to prospectively evaluate if the sensitivity and the specificity of extra- and intrarenal Doppler spectral analysis indexes are influenced in the diagnosis of renal artery stenosis by the kind of lesion: atherosclerotic (ARAS) or fibrodysplastic (FDRAS).
Peak systolic velocity (V), renal-aortic ratio (R), time of systolic acceleration (T), systolic acceleration (A), pulsatility index (PI) and resistance index (RI) were obtained in a series of hypertensive patients with atherosclerotic or fibrodysplastic renal artery stenosis that had been confirmed by renal arteriography.

Materials and Methods

Between January 2001 and March 2004, 155 hypertensive patients (79 males, 76 females; age range: 21-67 years; mean age: 46 ± 11 years) (310 kidneys) were enrolled in this prospective study.
Ninety-three had essential hypertension; the remaining 62 had secondary hypertension with unilateral (49/62 patients) or bilateral (13/62) renal artery stenosis.
Enrolment criteria included one or more clinical findings suggestive of renovascular disease: negative family history, abrupt onset of hypertension, onset of hypertension before age 30 or after 50, hypertension refractory to appropriate three-drug regimen, hypertension and unexplained impairment of renal function, severe hypertension (diastolic blood pressure greater than 120 mm Hg), accelerated or malignant hypertension, abdominal bruits, unilateral small kidney discovered by any clinical study, extensive occlusive vascular disease involving coronary, cerebral, and peripheral vessels and symptoms of arteriosclerotic disease, impairment of renal function in response to angiotensin-converting enzyme inhibitor (2,3). Color and duplex Doppler sonography and renal arteriography studies were with the informed written consent of the patients.
Examinations were made under blinded conditions.
To eliminate interobserver variability and the influence of equipment-related factors, all color Doppler studies and Doppler spectral analysis were performed by a single trained operator using a state-of-the-art scanner (AU5 Color Imaging, Esaote Biomedica, Genova, Italia) with a convex-array 2.5 MHz probe.
The Doppler frequency generally used was 2.5 MHz. The operator made at least 3 velocimetric measurements at the level of main renal artery and of the renal parenchyma, bilaterally.
A combined anterior and translumbar approach was used, with multiple longitudinal, transversal and oblique scans.
Patients were studied after a fast of at least 6-8 hours.
The patient was first studied in a supine position with the anterior approach and transversal epigastric scans to visualize the ostium and the proximal tract of the main renal artery.
The probe was positioned over the epigastric region and directed latero-laterally, toward one side, to visualize the contralateral renal artery.
The patient was then placed in the lateral decubitus position, and the ostium and the entire renal artery were studied using a translumbar approach (26-29).
The same approach allowed visualization of the renal parenchyma and intrarenal arteries.
Compared with the anterior approach, translumbar scans, with a frequency of 2.5 MHz and an angle of 45°, eliminated the problem of bowel-gas interference and thus allowed better visualization (particularly in obese patients) of the retroperitoneal arteries and renal vascular peduncle.
Adequate visualization of the renal arteries was of primary importance to demonstrate the presence and location of the stenosis and for correct positioning of the sample volume for direct velocimetric Doppler spectral analysis.
Color mode imaging, using an anterior approach, with the patient in the supine decubitus position, allowed adequate visualization of the renal artery in the vast majority of patients.
Segments displaying a colored mosaic pattern were carefully examined since there was a higher chance of detecting increased systolic and diastolic flow rates in these tracts.
When color aliasing or a color mosaic pattern in systole was detected (probable reflections of arterial narrowing), the sample volume was positioned in the area of color desaturation.
In the absence of abnormalities in the color patterns, the sample volume was positioned casually.
Color imaging, using the combined anterior and translumbar approach, was also used to identify accessory renal arteries.
When the main renal arteries were not clearly visualized, the operator checked for blood flow within the segmental intraparenchymal renal arteries. If there was no dectetable blood flow at this level, renal artery occlusion (100% stenosis) was diagnosed.
The velocimetric Doppler spectral analysis of the main renal arteries was performed with a Doppler-to-vessel angle of 30-60° and a sample volume size of 3 mm.
Wall filters (between 50 and 100 KHz) were required in a few cases to avoid pulsatility artifacts created at the level of the ostium.
The main renal artery and abdominal aorta were sampled with a pulse repetition frequency (PRF) of 3 MHz.
The following were considered direct signs of renal artery stenosis: increased peak systolic velocity (V) of the renal artery, expressed in cm/sec and evaluated after correction for the angle of insonation, and the renal-aortic ratio (R), calculated as the ratio between V and the peak systolic velocity of the abdominal aorta at the level of the renal artery or above its ostium.
The intrarenal Doppler spectral analysis indexes (T, A, PI, and RI) were measured by sampling the interlobar arteries contiguous to the middle pyramids, following reduction of the color repetition frequency to 800 Hz, reduction of duplex PRF to 1 KHz, and angular correction to a range of 25-30°.
Measurements of T and A were made as the slope of a

tangent to the steepest portion of the early systolic tracing (16,21).
The US examination was considered technically successful only when three consecutive velocimetric measurements were obtained at each of the following levels: the aorta, the renal arteries, and the intrarenal arteries.
The reproducibility of measurements of extra- and intrarenal Doppler parameters was evaluated using the same examination technique in a selected group of 5 consecutive hypertensive patients with normal renal arteriography who were not included in the present series.
During each examination, the patient's face was covered so that he/she could not be identified by the operator.
Using anterior and translumbar approaches, a total number of 9 samplings were obtained: three at the level of the suprarenal abdominal aorta, three at the level of the renal artery, and three at the level of the kidney.
Each sampling including 10 heart-beats.
Two separate examinations were performed, the second after an interval of at least 30 minutes.
Blood pressure was monitored throughout the examination.
The results of spectral analysis were recorded and analyzed retrospectively.
During the registration, the reference caliper measurements were made automatically, and the "auto-trace" function was used to a hard copy of the data set for each patient.
The distribution of the mean values of Doppler parameters and intraobserver variability for these values were expressed as coefficients of variation (CV%), calculated as *(SD/mean)*100* (30).
The resulting CV% values for each index were the following: 6.5% (V), 5.7% (R), 8.9% (T), 7.7% (A), 7.9 (PI) and 4.5% (RI).
The receiver operating characteristic (ROC) curves method was used to identify normal ranges for each quantitative index in all hypertensive patients included in our series: $V \leq 135$ cm/sec, $R \leq 2.71$, $T \leq 67$ ms, $A \geq 3.12$ m/sec^2, $RI \geq 0.60$ and $PI \geq 1.05$.
Using these cut-off values, we evaluated the sensitivity and specificity of each index in the detection of ARAS; the same analysis was performed for detection of FDRAS.
Atherosclerotic renal artery stenosis was defined as more than a 50% reduction in vessel caliber.
Although several attempts were made, it was more difficult to accurately measure the degree of narrowing of associated with fibromuscular dysplasia: no cut-off was therefore required for FDRAS.
The sensitivity and specificity various index combinations were assessed with "Multivariate General Linear Hypothesis Statistic Model" software (Systat 5.0, 1990).
Using Bayes theorem, adjusted positive and negative predictive values (PPV and NPV, respectively) for the most sensitive index were calculated based on prevalence values of ARAS and FDRAS (31).

Results

Renal arteriography allowed visualization of all 310 renal arteries: 235 were normal and 75 stenotic.
Among the latter, 46 (61%) had atherosclerotic stenosis (ARAS) and 29 (39%) fibromuscular dysplasia (FDRAS).
Unilateral stenosis, which was observed in 49 patients, was caused by atherosclerosis in 32/49 cases and fibrodysplasia in the remaining 17/49.
Thirteen patients had bilateral stenosis, atherosclerotic in 7/13 and fibrodysplastic in 6/13.
No occluded renal arteries were observed on arteriography. Bilateral V, R, T, A, PI, and RI values were measured in all cases. The mean time needed to measure V and R was 11±4 minutes, while measurement of T, A, PI, and RI required a mean of 6±3 minutes. Results, expressed as mean values ± SD and tested by Student's t-test, are reported in Table I. The sensitivity and specificity of each index and index combination for diagnosis of the two types of renal artery stenosis are reported in Table II.
Peak systolic velocity measured in the proximal tract of the main renal artery and time of systolic acceleration measured in the homolateral kidney were frequently increased due to the presence of ARAS (> 50%).
On the other hand, R allowed the correct diagnosis in one case of ARAS with normal V and in eight normal arteries with V values above normal. This ratio proved to be the most sensitive index for the detection of atherosclerotic stenosis: in fact, it was increased in all but 3/46 with this type of stenosis. The most sensitive intrarenal index was T: increased values were observed for all but 9/46 arteries with atherosclerotic stenosis and in only 40 of the 218 normal arteries. In the presence of FDRAS, both extra- and intrarenal indexes were frequently normal. The V and R indexes displayed low sensitivity and high specificity in the detection of FDRAS; the PI had similar sensitivity but lower specificity. The positive and negative predictive values of the R, adjusted for the prevalence of ARAS or FDRAS, are reported in Fig 1.
Multivariate analysis demonstrated that use of R with T, A, PI, and RI was less sensitive than R alone for the detection of ARAS, but this difference was not statistically significant. On the other hand, in the detection of fibromuscular dysplasia, the combined use of R and PI resulted in an increase in sensitivity, which was not statistically significant, and a decrease in specificity.

Discussion

Color duplex sonography is a relatively inexpensive diagnostic test, which can be used in all patients, regardless of their renal function status (6,9,13,14). Its main limitation in the study of renal artery stenosis is that it is difficult to perform and by no means rapid. These problems can be reduced by use of the translumbar approach (32-35).
Other limitations include insufficient visualization not only of the distal part of renal arteries and their branches but also of accessory renal arteries (19,20). In our experience, color duplex Doppler sonography always allows visualization of the origin and the proximal tract of the renal arteries, as well as the segmentary and interlobar arteries of the kidney.
Correct methodology includes the use of multiple approaches (anterior and translumbar) and multiple scan plans (transverse, longitudinal, and oblique), which results in a fairly lengthy examination (27-29). The advantage of this method is that

Tab. I. Doppler findings in 310 renal arteries of hypertensive patients. Mean value ± SD (**A**) and graphic representations (**B**) of extra- and intrarenal Doppler indexes measured in different groups of hypertensive patients (EH) and in patients with monolateral (M) and bilateral (B) atheromatous stenosis (ARAS or ATH) and fibromuscular dysplasia (FDRAS or FMD) of the renal arteries. ARAS or ATH (C) and FDRAS or FMD(C) indicate contralateral normal arteries in hypertensive patients with monolateral stenosis.

Table I. *Media dei valori ±DS (1 deviazione standard) (**A**) e grafico (**B**) di ciascun indice Doppler prossimale e distale ottenuta per i differenti gruppi di arterie renali nei pazienti ipertesi essenziali (EH) ed in pazienti con stenosi delle arterie renali monolaterali (M) e bilaterali (B) di tipo aterosclerotico (ARAS/ATH) e fibrodisplastico (FDRAS/FMD). Con ARAS/ATH (C) e FDRAS/FMD (C) sono indicate rispettivamente le arterie controlaterali normali nei pazienti ipertesi con stenosi monolaterale di tipo aterosclerotico e di tipo fibrodisplastico.*

(A)

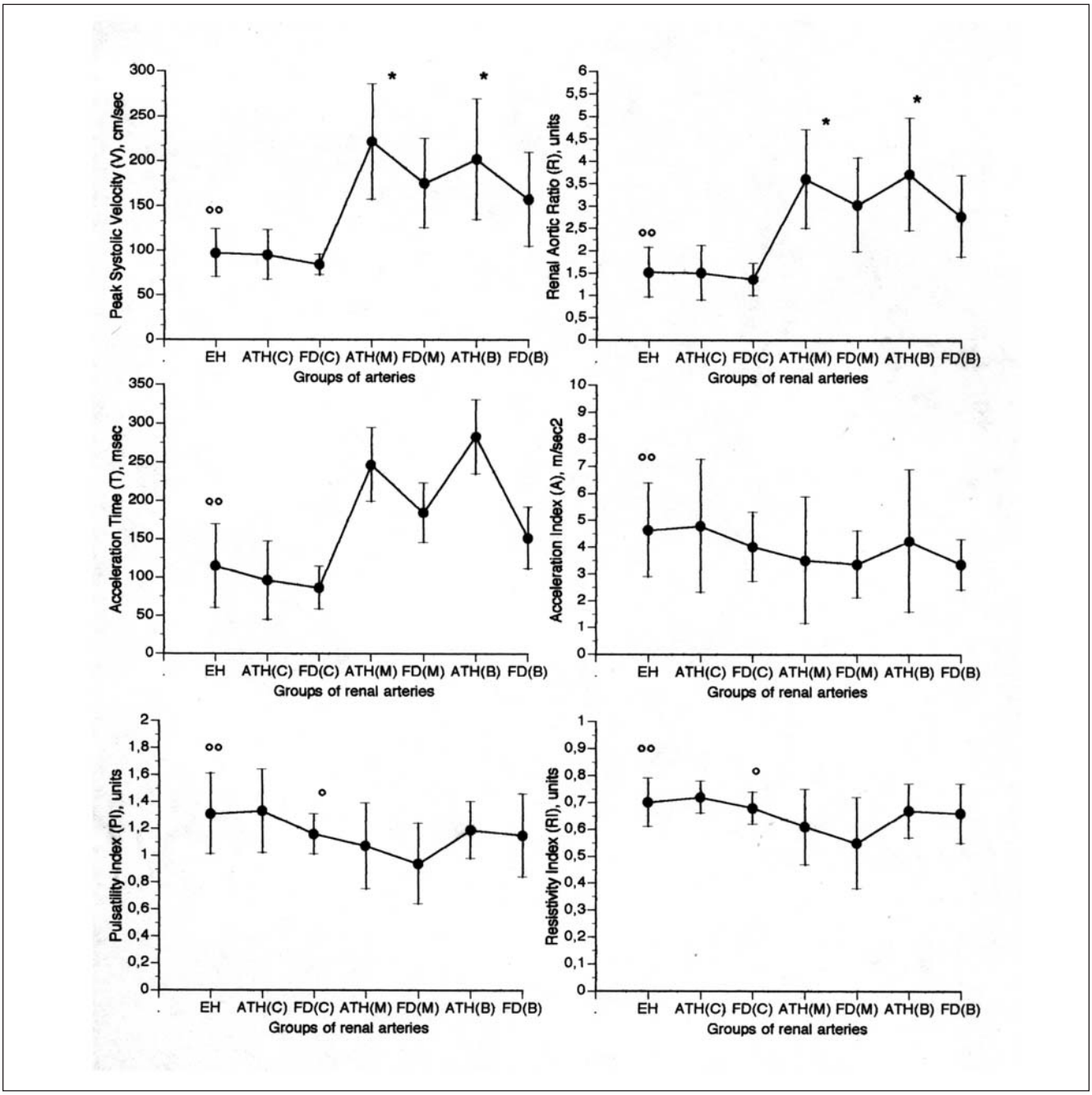
Doppler Indexes	Non stenotic arteries			Stenotic arteries			
	EH n=186	ARAS(C) n=32	FDRAS(C) n=17	ARAS(M) n=32	FDRAS(M) n=17	ARAS(B) n=14	FDRAS(B) n=12
(V) cm/sec	97.1±26°°	94.9±27.6	84.3±11.4	221.4±64*	175.1±50	201.8±67*	157±52.2
(R) units	1.52±0.5°°	1.51±0.61	1.36±0.36	3.6±1.1*	3.03±1.05	3.71±1.26*	2.78±0.91
(T) ms	114.4±54°°	95.6±51.2	86±27.8	246±40.3	184.1±38	282.5±60	151.3±40
(A) m/sec^2	4.63±1.7°°	4.79±2.47	4.02±1.3	3.51±2.37	3.37±1.25	4.23±2.65	3.37±0.94
(PI) units	1.31±0.3°°	1.33±0.31	1.16±0.15°	1.07±0.32	0.94±0.3	1.19±0.21	1.15±0.3
(RI) units	0.7±0.09°°	0.72±0.06	0.68±0.06°	0.61±0.11	0.55±0.17	0.67±0.1	0.66±0.11

Legend:

EH=essential hypertension; ARAS=atherosclerotic renal artery stenosis; C=contralateral; FDRAS=fibromuscular dysplastic renal artery stenosis; M=monolateral; B=bilateral; n=number of arteries; ± SD standard deviation;
°p=0.05; * and °°p<0.05.

accessory renal arteries originating close to the ostium of the main renal artery can be visualized. Quantitative evaluation of V and R can be technically challenging. In fact, reported figures on the feasibility of these measurements (58-95%), as well as their sensivity (0-100%) and specificity (37-100%) are characterized by substantial variability (19,20,22,27-28,35-48). ARAS generally involves the ostium and the proximal tract of the artery, producing marked narrowing of the vessel lumen. In contrast, fibromuscular dysplasia most frequently develops in the middle tract of the renal artery, may extend to the peripheral branches, and is often characterized by an association of stenosis and dilatations (1). Atherosclerotic stenosis was best detected in our series based on the R index. In patients with FDRAS, V values are not always increased, and this explains the relatively low sensitivity of V and R indexes in demonstrating the presence of hemodynamically significant FDRAS in our series. However, the flow-rate differences between atherosclerotic and fibromuscular dysplastic vessels reflect their different anatomo-pathologic characteristics. In FDRAS a more limited increase in blood flow velocity is to be expected due to the presence of dilatations. Moreover, the disease affects the distal portion of the artery, where visualization of the mosaic pattern and aliasing artifacts is difficult. The intrarenal indexes can be measured in a higher percent of cases (reported range: 98-100%) (21, 23-24,49-54). In previous studies, the sensitivity (range: 57% to 100%) and specificity (range: 48% to 95%) of these indexes were found to be equal to or higher than those of V and R (9,15,16,23,26). Differences between the two kidneys in terms of PIs (ΔPI > 12%) and RIs (ΔRI > 5%) can reportedly correct false negative diagnoses, thereby increasing the sensitivity of PI (94%) and RI (82%) (21,23). Several factors may explain the low sensitivity of

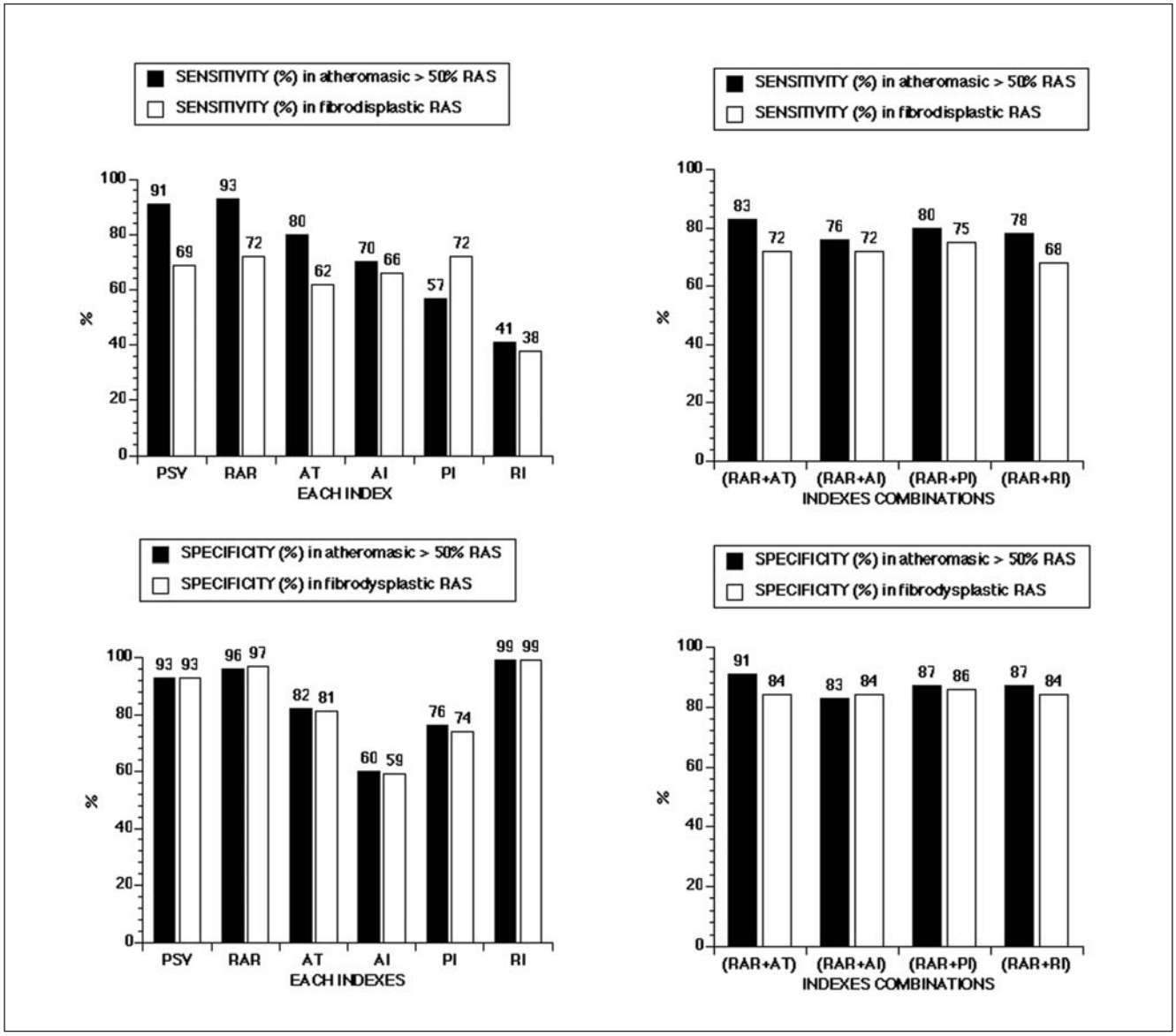
(B)



Legend:

EH=essential hypertension; ATH=atherosclerotic renal artery stenosis; C=contralateral; FD=fibromuscular dysplastic renal artery stenosis; M=monolateral; B=bilateral; °p=0.05; * and °°p<0.05.

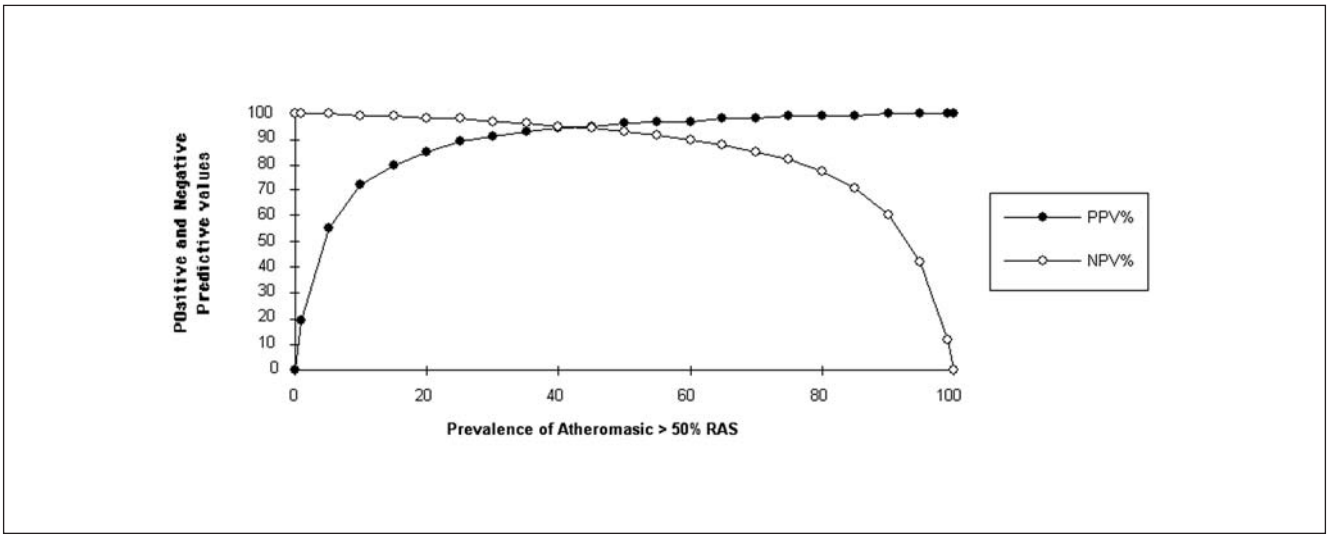
Tab. II. Sensitivity (SENS) and specificity (SPEC) (%) of each Doppler spectral analysis index (PSV, RAR, AT, AI, PI, RI) and index combinations in the detection of atheromatous (>50% narrowing) or fibrodysplastic renal artery stenosis (RAS).
Table II. *Sensibilità (SENS), specificità (SPEC) in valore percentuale (%) di ciascun indice velocimetrico Doppler extra- o intrarenale (PSV, RAR, AT, AI, PI, RI) preso singolarmente o in combinazione nei pazienti con stenosi renale (RAS) di tipo aterosclerotico >50% o fibrodisplastica.*



Legend:

RAS=renal artery stenosis; PSV=peak systolic velocity; RAR=renal-aortic ratio; AT=acceleration time; AI=acceleration index; PI=pulsatility index; RI=resistance index

(A)



(B)

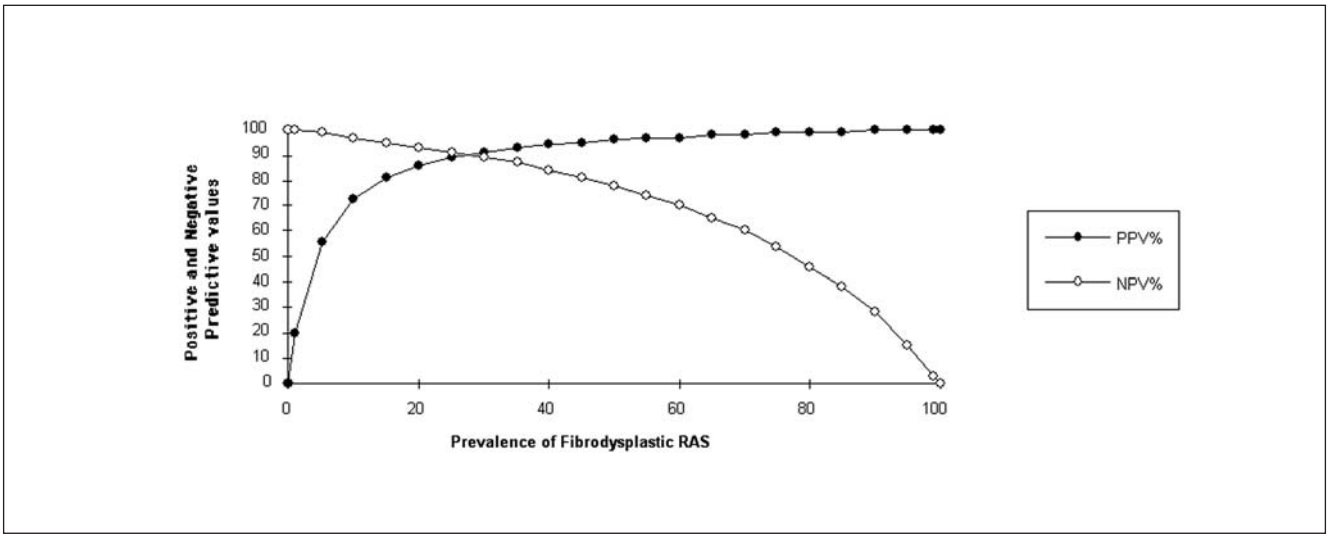


Fig. 1. Color duplex Doppler sonography. Renal aortic ratio (R). Relationship between positive predictive value (PPV), negative predictive value (NPV), and prevalence of renal artery stenosis (RAS). (**A**): sensitivity 93%, specificity 96%, Positive (PPV) 84% and Negative (NPV) 99% Predictive Values according to the prevalence of atheromatous RAS (> 50%). (**B**): Sensitivity 72%, Specificity 97%, Positive (PPV) 75% and Negative (NPV) 96% Predicitve Values according to the prevalence of fibrodysplastic RAS.

Figure 1. *Ecografia color duplex Doppler. Rapporto renale-aortico (R). Relazione tra il valore preditivo positivo (PPV) e valore predittivo negativo (NPV) e prevalenza di stenosi dell'arteria renale (RAS).* (***A***)*: sensibilità 93%, specificità 96%, valore predittivo positivo (PPV) 84% e valore predittivo negativo (NPV) 99% in accordo con la prevalenza di stenosi renale aterosclerotica >50%.* (***B***)*: Sensibilità 72%, Specificità 97%, valore predittivo positivo (PPV) 75% e valore predittivo negativo (NPV) 96% in accordo con la prevalenza di stenosi fibrodisplastica.*

the intrarenal Doppler spectral analysis indexes in detecting the presence of atherosclerotic and fibromuscular dysplastic lesions in our series. In the first place, we defined ARAS as vessel narrowing of > 50%, whereas in angiographic studies, stenosis is defined as significant when it is >60%. Moreover, no cut-off was required for FDRAS, so our series included FDRAS cases with less than 50% narrowing. It is not surprising, therefore, that the sensitivity for FDRAS proved to be rather low.

Some reports have shown that the sensitivity and specificity of the intrarenal indexes may vary depending on the degree of stenosis (measured angiographically) (24,38,55).

In contrast, some Authors have demonstrated that the results of waveform analysis are characterized by acceptable interobserver agreement, but this parameter is not correlated with either the presence or severity of renal artery stenosis (16,56). It is important to recall, however, that renal ischemia and hypertension are not a risk until at least 75% of the lumen has been occluded, but correlation between the arteriographic appearance and the degree of ischemia is poor. While duplex scanning may be able to demonstrate the presence of renal artery stenosis, it can provide no information on the effects of the stenosis on the kidney (2).

The low sensitivity of the intrarenal indexes may also be due to excessively high cut-off values for T, A, PI and RI. The presence or loss of the early systolic peak depends on complex interaction between the degrees of vascular compliance and resistance (16,57). Arterial compliance is a function of age (5). Cut-off values of RI are very high in our series providing for low sensitivity and high specificity in both atherosclerotic and fibrodysplastic stenoses. The PI was more sensitive for detection of FDRAS, although it displayed almost identical levels of specificity for ARAS and FDRAS. It must be stressed that, in our patients with unilateral FDRAS, the mean RIs and PIs for the normal contralateral artery were significantly lower (p=0.05) than those recorded for patients with unilateral ARAS. This finding is due to the fact that the FDRAS patients were younger than those with ARAS. Finally, we chose to position the sample volume on a single intrarenal vascular bed (interlobar artery) for measurement of both acceleration and resistance indexes. This method differs from that reported by other authors, who measure acceleration indexes in the segmentary arteries and resistance indexes in both the segmentary and interlobar arteries (17,24,38). Our preference for sampling the interlobar arteries is due to their fixed anatomy adjacent to the renal pyramid, which improves the reproducibility of measurements and facilitates repeat measurements.

The precise significance of each intrarenal index is still debated (50-54). This is also due to the influence of factors such as the alterations in vascular resistances, which can be caused by pharmacological treatments, acute and chronic renal disease, cardiac output, age, duration and severity of hypertension. The presence of systemic vascular disorders or parenchymal renal diseases may alter the resistance of the renal vascular bed (58-67). In conclusion our study proves that the sensitivity and specificity of color Doppler and Doppler spectral analysis sonography indexes in the diagnosis of renal artery stenosis may vary depending on the nature of the stenosis (ARAS vs. FDRAS).

In our experience, these indexes are more valuable in detecting atherosclerotic stenosis than fibromuscular dysplasia. An increased R value is the most useful index for diagnosing atherosclerotic stenosis. However, even with carefully selected patients, the sensitivity of color Doppler and Doppler spectral analysis are still low sensibility.

This is particularly true for hypertensive patients with fibromuscular dysplasia. Our results therefore strongly suggest that color duplex Doppler sonography is a valid diagnostic test for the detection of renal artery stenosis in a selected population of hypertensive patients.

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