New intrarenal echo-Doppler velocimetric indices for the diagnosis of renal artery stenosis

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We aimed at comparing the positive and negative predictive values (PPV, NPV) of several intrarenal velocimetric indices for revealing the presence of renal artery stenosis (RAS) among hypertensive patients who underwent a renal angiography for the clinical suspicion of renovascular hypertension. In 106 patients (200 kidneys), the pulsatility index (PI) and resistive index (RI), the acceleration time (AT), and the mean systolic acceleration (ACC_{sys}) were evaluated. In addition, the maximal systolic acceleration (ACC_{max}), that is, the maximal slope of the acceleration phase, and the maximal acceleration index (AI_{max}), that is, the ratio between ACC_{max} and the relative peak systolic velocity, were calculated. On angiography, we found that 56 (28%) of the 200 arteries had a greater than 60% RAS. PI and RI had an NPV below 75%, whereas AT, ACC_{sys}, ACC_{max}, and AI_{max} had an NPV always above 95%. However, ACC_{max}, and AI_{max}, at their best cutoff limits, had higher PPV than ACC_{sys} and AT (60 and 70% vs 45 and 51%, respectively). Thus, in a cohort of patients with a high prevalence of RAS, PI and RI failed to reach an NPV adequate for a screening test. In contrast, all the acceleration indices we tested had a sufficiently high NPV but AI_{max} appears superior to the others because of higher PPV. We propose the evaluation of AI_{max} as an additional screening test in patients with hypertension and the clinical suspicion of RAS.

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In recent years, it became increasingly appreciated that renal artery stenosis (RAS), apart from being responsible for the elevation of blood pressure in some patients, can cause a chronic ischemic nephropathy with a progressive loss of renal function that eventually leads to end-stage renal disease.[1,2] Moreover, percutaneous transluminal renal angioplasty alone or in combination with stent implantation has progressively emerged as a reliable method for treating both renovascular hypertension and ischemic nephropathy even in those patients, like the elderly, in whom the conventional surgical treatment is not feasible because of the exceedingly high risk.[3] Not surprisingly, there has been increasing interest in developing screening tests capable of accurately detecting the presence of RAS and also of evaluating its functional consequences in order to select patients who may actually benefit from dilation procedures.[4]

In this respect, already in the early 1990s, the duplex-Doppler ultrasound examination of the renal artery has attracted attention because, apart from being non-invasive, repeatable, and of relatively low cost, it combines the ability of visualizing the RAS with that of determining the alterations in renal blood flow through the measurement of the velocimetric indices.[5,6] Yet, the initial enthusiasm toward this technique has been tempered by the technical difficulties encountered in measuring the so-called 'proximal' velocimetric indices, that is, those sampled just at the site of the arterial narrowing. Although specific, this approach has low sensitivity, is highly operator and technical equipment dependent and is afflicted by a high drop-out rate of unsuccessful investigation because of obesity, abdominal gas, or unlucky scan window, limitations that led, in earlier studies, to a low accuracy in detecting significant RAS.[7,8] However, more recent investigations, one of which was performed with contrast enhancement, yielded significantly better results.[9,10]

An alternative approach substantially devoid of technical drop-out has been that of performing the sampling of blood flow velocity at the renal hilum or in the intraparenchymal arteries with the so-called 'distal' indices. These latter

measurements, including the pulsatility and resistance indices (PI and RI), the mean systolic acceleration (ACC_{sys}), and acceleration time (AT), have the advantage of circumventing some of the problems related to the proximal ones, in that being easily sampled distally to RAS allow the evaluation of damping in kinetic flow energy and pulse wave transfer at any level of the arterial trunk.[11]

PI and RI had been extensively applied at first,[12–14] but a comparative study of ours[15] indicated that ACC_{sys} and AT may be superior to PI and RI in detecting a significant RAS. In another study,[16] the combination of PI and AT has been shown to further improve the diagnostic accuracy of echo-Doppler investigation. Along this line, Radermacher *et al.*[17] have shown that in main renal arteries in which the proximal indices could not be determined, the evaluation of AT made the detection of RAS always possible. As a result, the approaches at the extrarenal and intrarenal vasculature may be seen as complementary rather than as an alternative.[18]

Yet, a potential source of bias even in the measurement of ACC_{sys} and AT is represented by the shape of the Doppler spectra, which, even when sampled from a normal artery, are far from being uniform.[19] Herein, we examined the possibility of circumventing this bias by focusing on the evaluation of acceleration in the early systolic phase, namely in the initial part of the curve, which is more uniform; to do so, we introduced as a new index the maximal systolic acceleration (ACC_{max}) (see Materials and Methods and Figure 1). In addition, as even in normal kidneys the acceleration drops, going from the proximal to the distal vessels, we attempted to generate comparable measures independently from the different levels of the vascular tree where the Doppler spectra are sampled, introducing another new index, that is, the maximal acceleration index (AI_{max}), in order to correct the acceleration for the absolute flow regimen.

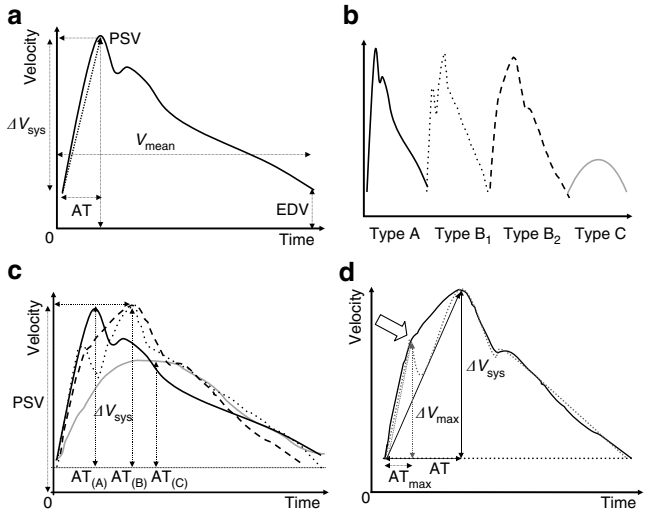

Figure 1 | (a) Analysis of the Doppler spectra. From this, the following hemodynamic parameters can be derived: PSV, EDV, the averaged mean velocity (V_{mean}) AT taken as the time from the beginning to the peak of the systole; ΔV_{sys} indicates the velocity gradient between the foot and the peak of the systolic phase. From these parameters, the conventional distal Doppler velocimetric indices, that is, PI, RI, and the mean acceleration ACC_{sys}, are calculated as reported in the text. (**b**) Heterogeneous velocity cycle slope morphologies that can be found in normal and stenotic renal arteries. The type 'A' morphology has a constant systolic acceleration until the systolic peak and it is characteristic of a normal hemodynamic pattern. However, in normal and stenotic arteries also the 'B_1' and 'B_2' morphologies can be found, characterized respectively by a double peak during the systolic acceleration and by a shoulder that divides the early steeper acceleration from the late, less steep phase. The type 'C' morphology is characterized by a flattered cycle with a rounded systolic shape and is typical of a post-stenotic flow regimen. (**c**) Illustration of how the cycle morphologies can affect the calculation of velocimetric indices. It is obvious that in normal arteries both B type morphologies can cause a delayed AT resulting in dampened ACC_{sys}, mimicking a condition similar to that found in stenotic arteries (type C morphology). (**d**) Illustration of how the new indices proposed in this study can improve the diagnostic accuracy in arteries with type 'B' morphology. Focusing on the estimation of the acceleration in the early systolic phase, we derived the maximal systolic acceleration ($ACC_{max} = \Delta V_{max}/AT_{max}$) defined as the mean slope of the systolic acceleration until any significant change of its first derivative has been introduced (white arrow). Moreover, by correcting the acceleration for the relative absolute velocity regimen, which may differ at different levels of the renal vascular tree, we derived the maximal acceleration index ($AI_{max} = ACC_{max}/PSV$).

RESULTS

Angiographic and clinical data

According to the instructions described below, the correct measurements of the conventional and new velocimetric indices were made in a total of 106 patients (12 with a single kidney) for a total of 200 kidneys.

On angiography, 57 of these 106 patients were found to have a RAS; of these, 15 had a bilateral lesion and 42 a unilateral RAS (in 10 cases, in a solitary kidney) for a total of 72 RAS. In the remaining 49 patients (two with a single kidney), no RAS was observed on angiography; thus, including the contralateral non-stenotic kidneys, a total of 128 normal kidneys were examined. The degree, site, and type of the RAS are illustrated in Figure 2. In 56 out of the 72 RAS the arterial narrowing was $\geqslant$60%, whereas in five it was less than 50%, and in the remaining 11 it was between 50 and 59%; thus, in our population, the pre-test probability for a significant RAS was 28%. The majority of RAS were atherosclerotic and located at the ostium of the artery, whereas the fibromuscular ones were mostly located in the trunk of the renal artery but without any difference in terms of stenosis significance distribution.

The demographic and most relevant clinical data of patients with and without angiographically proven RAS are reported in Table 1. The only significant difference between these two subgroups was in serum creatinine because of the inclusion among the patients with RAS of those with bilateral stenosis.

Echo-Doppler velocimetric data

All velocimetric indices were significantly different in renal arteries with RAS with respect to the group including arteries without RAS and with less than 60% RAS (Table 2).

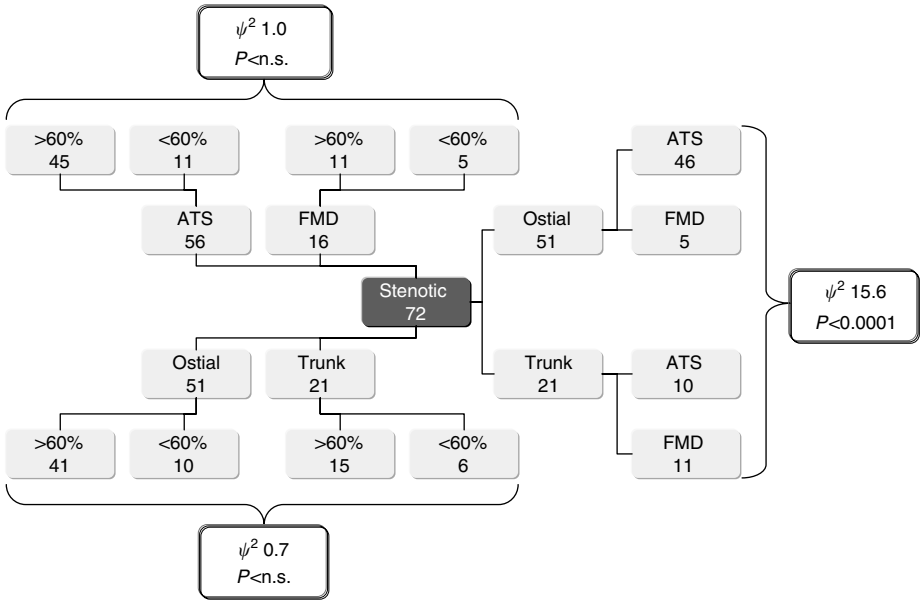

Figure 2 | Distribution of the 72 stenotic kidneys with respect to the site, type, and severity of RAS. As expected, there was a prevalence of fibromuscular RAS in the renal artery trunk in comparison with atherosclerotic RAS, which was more frequently located at the ostium; between the two types of RAS, there were no significant differences in the severity of the stenosis.

Table 1 | Clinical and laboratory data of patients who were included in the database for the calculation of echo-Doppler velocimetric indices (mean ± s.d.)

	Without RAS n=49	RAS of any degree n=57	$P<$
Age (years)	55 ± 13	57 ± 16	NS
Gender	14F/35M	22F/35M	NS
SBP (mmHg)	165 ± 23	168 ± 25	NS
DBP (mmHg)	99 ± 14	98 ± 16	NS
HR (beats/min)	74 ± 12	75 ± 14	NS
Serum creatinine (mg/dl)	1.0 ± 0.5	1.5 ± 0.8	0.01
Serum K+ (mEq/l)	4.3 ± 0.4	4.3 ± 0.5	NS
Serum glucose (mg/dl)	100 ± 18	94 ± 24	NS
Total cholesterol (mg/dl)	219 ± 44	222 ± 38	NS

DBP: diastolic blood pressure; F: female; HR: heart rare; M: male; NS: not significant; RAS: renal artery stenosis; SBP: systolic blood pressure.

Table 2 | Velocimetric indices in renal arteries with and without significant RAS

	Significant stenosis	ANOVA	Without significant stenosis
PI	0.98 ± 0.50	$P<0.02$	1.12 ± 0.33
RI	0.57 ± 0.012	$P<0.01$	0.63 ± 0.09
AT (ms)	152 ± 68	$P<0.0001$	79 ± 49
ACC_{sys} (m/s^2)	1.80 ± 1.52	$P<0.0001$	5.76 ± 3.96
ACC_{max} (m/s^2)	2.25 ± 1.78	$P<0.0001$	7.09 ± 3.68
AI_{max} (s^{-1})	6.00 ± 3.22	$P<0.0001$	14.03 ± 4.96

ANOVA: analysis of variance; PI: pulsatility index; RI: resistive index; AT: acceleration time; ACC_{sys}: mean systolic acceleration; ACC_{max}: maximal systolic acceleration; AI_{max}: maximal acceleration index.

However, as illustrated in Figure 3, for both PI and RI, there was a large overlapping between values observed in the three subgroups of arteries, leading to a rate of false positive and negative examinations, which was about 50% for the cutoff of 1.00 and 0.60, respectively.

The diagnostic accuracy of ACC_{sys}, AT, ACC_{max}, and AI_{max} for the best thresholds reported in Table 3 was clearly better than that of PI and RI. Indeed, because of the high sensitivity, the negative predictive values (NPV) of all these indices were always $\geqslant$95%. For ACC_{sys} and AT, the rate of false positives was 44 and 35%, respectively, as illustrated in the upper panels of Figure 4, which report the percent distribution of these indices in non-stenotic arteries. The cause of this still high false positive rate is made apparent in the upper panels of Figure 5, where non-stenotic arteries with type B cycle morphology contributed significantly to generate abnormal values, leading to a false diagnosis of RAS. ACC_{max} and AI_{max}, being less biased by the morphology of the velocity curve waveform and correcting for the angle beam estimation, at the best cutoff values of 4.0 m/s^2 and 9.0 s^{-1} further reduced the false positive rate to 25 and 16%, respectively (Figures 4 and 5, lower panels). As a result, the positive predictive values (PPV) of ACC_{max} and AI_{max} were 60 and 70%, respectively, that is, higher than those of ACC_{sys} and AT (45 and 51%, respectively). In addition, AI_{max} was not affected by the scan site, whereas all the other indices of acceleration were significantly lower when sampled in the interlobar arteries with respect to the pre-hilar tract of the renal artery (Figure 6). Moreover, AI_{max} was not affected by the etiology and by the location of RAS (analysis of variance F-value = 0.33 and 3.21, $P\leqslant0.57$ and 0.08, respectively). However, no significant correlation was found between AI_{max} or any of the other indices and the degree of the stenosis.

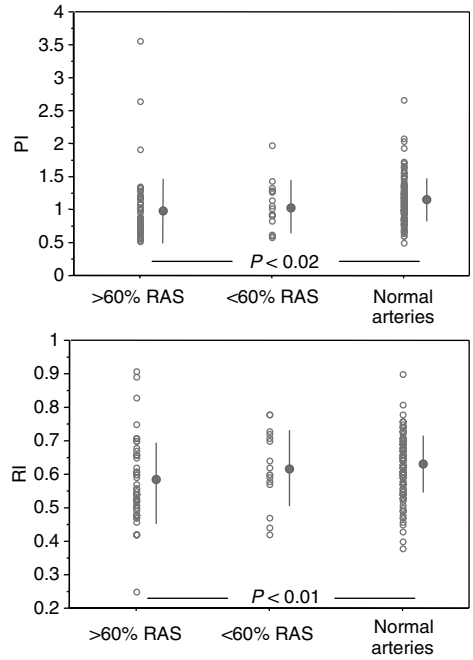

Figure 3 | Scatter distribution of the pulsatility and resistive indices (PI and RI) and their mean (±s.d.) values sampled in parenchymal arteries in kidneys without RAS and with significant and not significant RAS. A large overlapping between the three subgroups of arteries is evident.

Table 3 | Sensitivity, specificity, PPV, and NPV of the four acceleration-derived indices calculated for the ideal cutoff limits established with the ROC curve

	AT	ACC_{sys}	ACC_{max}	AI_{max}
Best cutoff	80 ms	4.0 m/s^2	4.0 m/s^2	9.0 s^{-1}
Sensitivity (%)	93	93	94	93
Specificity (%)	65	56	75	84
PPV (%)	51	45	60	70
NPV (%)	96	95	97	97

ROC curve: receiver operating characteristic curve; PPV: positive predictive value; NPV: negative predictive value; for other abbreviations, see Table 2 footnote.

The sensitivity and specificity of AI_{max} at the best cutoff value of 9.0 s^{-1} were also calculated for the 67 arteries with a greater than 50% stenosis, and stratified according to the degree of RAS. These were found to be respectively 88 and 89% for the stenosis $\geqslant$50%, 93 and 84% for those $\geqslant$60 and 92, and 82% for those $\geqslant$70%; the respective PPV and NPV were 80 and 94%, 70 and 97%, and 64 and 97%.

DISCUSSION

Since the introduction of ultrasonography into the field of hypertension, several velocimetric indices have been examined in the search for a reliable first-line screening test of RAS. Several scientific reports ranged from very poor to exciting results,[5–10] but, so far, it is still unclear which indices have the best accuracy and where, along the renal circulation, they should be measured.[20–23] Some recent studies[9,10] have shown that the diagnostic accuracy achievable with the

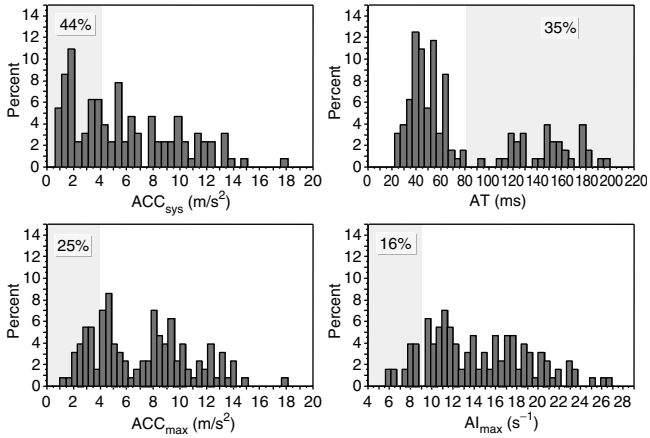

Figure 4 | Histogram distribution of ACC_{sys}, AT, ACC_{max}, and AI_{max} in the 144 renal arteries with no RAS ($n = 128$) and with not significant RAS ($n = 16$). The gray area includes the false positive studies, which are clearly reduced with ACC_{max} and even more so with AI_{max} (abbreviations are as in the text).

proximal indices is substantially better than that obtained in earlier investigations; yet, the so-called distal indices appear preferable to the proximal ones, mostly because the interrogation of the renal vessels at the parenchymal site reduces the technical difficulties inherent in the ultrasound method, making the examination feasible in almost all patients and relatively less time consuming.[12,24,25] Among the distal indices, we previously found that ACC_{sys} and AT were clearly superior to PI and RI in detecting both atherosclerotic and fibromuscular RAS, with an overall diagnostic accuracy of 85%, but these results were obtained in selected population of hypertensive patients with a very high prevalence of RAS.[15]

The multicentric study of the Italian Group for Renovascular Hypertension offered us the opportunity of extending that previous observation in a larger population of hypertensives and of refining the evaluation of the distal velocimetric indices in order to further improve their ability to detect a significant RAS.

In agreement with our earlier study, we found that for PI and RI, the overlap of values observed in kidneys with and without RAS was clearly greater than that of ACC_{sys} and AT. The most likely reason for this discrepancy is that the alterations of ACC_{sys} and AT induced by RAS are less affected than those of PI and RI by the concomitant impairment of renal parenchymal blood flow. Indeed, as the latter indices express a ratio between the maximal and minimal velocities across the arterial narrowing, the high intrarenal resistance may counterbalance the pressure gradient induced by RAS, whereas ACC_{sys} and AT are solely dependent on the maximal velocity of flow and on the time to peak systolic velocity as determined by the delayed pulse wave transfer across the stenosis and/or by the post-stenotic paradoxical increase of the arterial compliance.[19,26] This interpretation is supported by the notion that in normal arteries, values of PI and RI are correlated to the renal vascular resistance[27] and to the age of

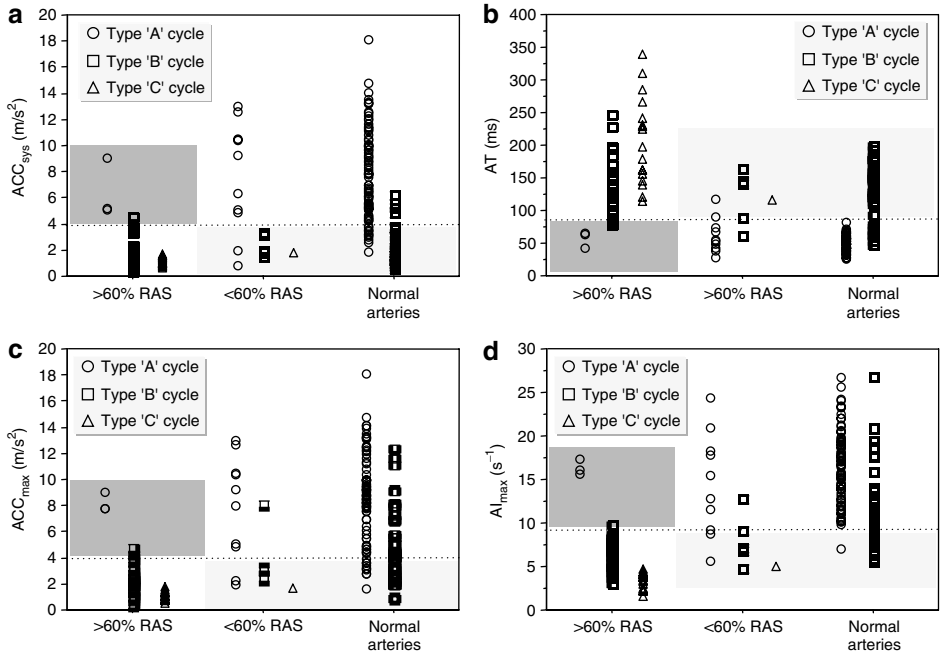

Figure 5 | Scatter distribution of (a) ACC$_{sys}$, (b) AT, (c) ACC$_{max}$, and (d) AI$_{max}$ values sampled in stenotic and non-stenotic kidneys in the parenchymal arteries. The dotted line represents the ideal cutoff values calculated for each index with the ROC curve analysis, whereas the gray and less gray areas include the false negative and false positive studies subdivided according to the cycle morphology curve described in Figure 1. For all indices, the rate of false negatives is obviously lower than that of PI and RI shown in Figure 3. Note that the majority of the false positive studies are attributable to arteries with type B cycle morphology and that erroneous diagnoses are reduced with ACC$_{max}$ and AI$_{max}$ (abbreviations are as in the text).

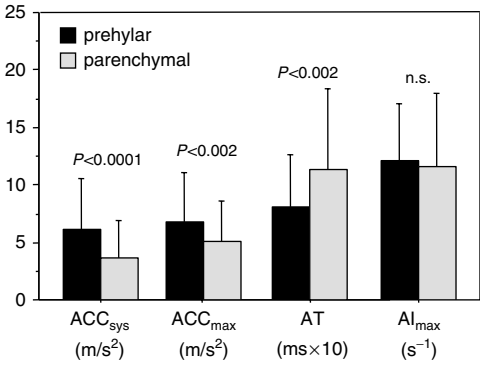

Figure 6 | Values of ACC$_{sys}$, AT, ACC$_{max}$, and AI$_{max}$ sampled at the pre-hilar and parenchymal sites. For all indices except AI$_{max}$, there were significant differences between (mean ± s.d.) the two sites of sampling as a result of the hemodynamic gradient along the renal circulation. Figures on the vertical axis refer to the units used to calculate the indices shown on the horizontal axis.

patients,[28] whereas no such correlation was found for ACC$_{sys}$ and AT.[15] Moreover, we have previously shown that in kidneys with atherosclerotic RAS, the alterations in PI and RI were less pronounced than those in ACC$_{sys}$ and AT, whereas this did not occur in younger patients with fibromuscular RAS, indicating that PI and RI also have the disadvantage of being affected by the etiology of stenosis.[15] Thus, the practical conclusion that can be drawn from the more extensive findings of the present study is that the diagnostic accuracy of PI and RI is unacceptably low for a screening test of RAS, although these indices maintain their validity for estimating the district vascular impedance in non-stenotic kidneys[27,29] or in stenotic kidneys for evaluating the degree of nephrosclerosis, as a prognostic sign of poor clinical outcome after angioplasty.[30]

However, not even ACC$_{sys}$ and AT are entirely satisfactory in that, in spite of their excellent NPV, we found in non-stenotic kidneys a heterogeneous distribution of Doppler cycle morphologies, with a substantial percent of type B curves mimicking the 'pulsus tardus' pattern typical of the stenotic ones; as a consequence, values of AT had a bimodal distribution, which explains the false positives observed even with this index. The same limitations apply to ACC$_{sys}$, whose values are additionally affected by the flow regimen at the scan site and by the scan angle.

Results of this study provide evidence that by focusing on the evaluation of acceleration in the early systolic phase, namely in the initial part of the curve, which is more uniform, by calculating the ACC$_{max}$, most of the biasing factors due to the cycle morphology can be circumvented. Further correction for the flow regimen, as stated by the peak systolic velocity, resulting in the calculation of AI$_{max}$ can also overcome the bias due to different scan site or wrong angle beam correction. Indeed, for the ideal cutoff values, the PPV of ACC$_{max}$ and AI$_{max}$ rose to 60 and 70%, respectively, maintaining an NPV of 97% for both. It is of interest that the sensitivity, specificity, PPV and NPV of AI$_{max}$ were essentially similar for all RAS above 50%, thus making this index useful for detecting even relatively mild narrowing of the renal

arteries. These PPV are nevertheless lower than those found for AT (91%) in the study of Burdick *et al.*,[15] but it must be appreciated that the predictive values are highly dependent on the prevalence of the disease in the population under investigation and that in that study the pre-test probability of RAS was 75%, whereas in this study it was remarkably lower (28%). Also, at variance with Burdick's study, no correlation was found between AT and any of the new indices and the degree of arterial narrowing. One possible explanation is that, in this study, the proportion of patients with an atherosclerotic RAS, in whom this correlation was found to be much weaker than that in fibromuscular RAS, was 78 against 57%.

The results of the present study are very similar to those of Johansson *et al.*[16] whose Doppler measurements reached an NPV and PPV of 97 and 71%, respectively, in a population of hypertensive patients with a prevalence of RAS of 19%; however, in their study, such a high NPV was obtained by combining the measurement of acceleration with that of the side-to-side difference of PI. Moreover, in their protocol, the Doppler evaluations were made in the interlobar renal arteries where the systolic acceleration is obviously lower than that in the main or segmental renal artery. Thus, the ideal cutoff values proposed by these investigators are applicable only to a specific site of the renal arterial tree; this limitation does not apply to AI_{max}, the values of which are already adjusted for the different sites of interrogation of the velocity spectra (see Figure 6).

One limitation of this investigation is that because of the study design, no comparative analyses of the new indices and of the proximal ones were performed; thus, it cannot be established from the present data which of the two approaches is superior. However, future studies exploiting the advantages of ACC_{max} and AI_{max} might explore to what extent their evaluation in combination with that of the proximal indices can further improve the accuracy of ultrasound examination in detecting a significant RAS.

A final consideration pertains to the applicability of these new indices to the 'real life conditions' in which these ultrasonographic investigations are usually performed. The time required to perform such detailed interrogations of renal arteries was 32 min, and this may be the limiting factor in the daily schedule of a busy ultrasonographer; yet, it is worth recalling that limiting the investigation to parenchymal vessels and restricting the calculation just to the two new indices may reduce the time required for each procedure, on average, to less than 15 min.

In conclusion, in a cohort of hypertensive patients with a 28% prevalence of greater than 60% RAS, PI and RI had an NPV too low to make these indices useful as a screening test. In contrast, all the four acceleration indices we tested had a very high NPV but only AI_{max} had a sufficiently high PPV. Thus, AI_{max}, owing to its ability to overcome the factors biasing the Doppler evaluation, appears superior to the other distal indices and promising as a screening test in patients with the clinical suspicion of RAS.

MATERIALS AND METHODS

Patients and protocol

This study is a subproject of a larger prospective study on the prevalence, diagnosis, and treatment of renovascular hypertension undertaken by the Italian Group for the Study of Renovascular Hypertension under the auspices and the direction of the Italian Society of Hypertension. Nineteen Italian Hypertension Units participating in the study recruited a total of 459 hypertensive patients who were admitted to the hospital for the strong clinical suspicion of renovascular hypertension, as indicated in detail elsewhere.[31]

In short, patients of both genders and without limitation of age and of concomitant conditions except advanced cancer and pregnancy were admitted to the study. Whenever it was ethically possible, 2 weeks before admission and during the study period patients underwent a wash-out of the antihypertensive treatment they were on; when this was not feasible, care was taken to use calcium channel blockers and alpha-blockers to control blood pressure, unless the abstinence from other medications was considered clinically dangerous.

The protocol included a daily blood pressure monitoring, the collection of peripheral blood sample for the evaluation of a complete biochemical profile, a urine analysis, and the evaluation of target organ damage estimated with an EKG and with a cardiac echo-Doppler. In addition, patients underwent numerous investigations aimed at detecting the presence of RAS; these included the determination of plasma renin activity and plasma aldosterone, a renal scintigraphy, a computed axial tomography and a three-dimensional magnetic resonance and an echo-Doppler velocimetry of renal arteries. Each procedure was performed by an independent operator who was unaware of the outcome of the others.

In order to standardize the results obtained by different operators, all centers received detailed instructions on how to perform the various procedures, which were executed depending on the facilities available in each center and according to the sequence selected by the physician in charge. However, as a final investigation and independently from the results of the previous ones, all patients underwent a conventional renal angiography or aortography, the results of which were taken as reference for confirming or denying the presence of RAS.

The angiography was performed taking at least two views of all arteriograms to assess the severity of RAS. The degree of the arterial narrowing was estimated visually by the responsible radiologist of each center. In the light of the known discrepancies in RAS reports among different observers,[32] all involved radiologists were instructed to classify the RAS as atherosclerotic or fibromuscular and, according to its localization, as ostial/paraostial, median, or distal. The severity of RAS was estimated comparing the caliber of the vessel at its narrowest point to that distal to the stenosis just before the bifurcation, and the degree of narrowing was categorized as below 50%, 50–59, 60–69, 70–79, 80–89, and 90% or more. Owing to the known difficulties in evaluating the RAS of the polar renal arteries, the radiologist's reports were confined to the description of the main renal arteries.[33] On the basis of some recent ultrasonographic studies,[9,34,35] a narrowing of the renal artery equal or greater than 60% was taken as a cutoff value to define a RAS as hemodynamically significant.

Echo-Doppler technique

All participating centers received detailed instructions in order to standardize this procedure (see below). As this study was designed to prospectively mirror the routine investigation of this kind of

patients, each center was left free to perform the echo investigation according to the skill of the local physician/ultrasonographer and the available facilities. Thus, only in six centers, it has been possible to measure the early systolic acceleration phase, the cycle type, and the calculation of ACC_{max} and the relative AI_{max} as indicated below.

All patients were investigated in a blind manner with respect to the other diagnostic procedures including angiography and, whenever possible, at the end of the pharmacological wash-out period. Patients were investigated in the morning in the fasting state after at least 30 min in a recumbent position, with scan window in a semilateral position at the subcostal or lateral projection. The coronal or longitudinal scan of the kidney was adjusted with minimal depth to emphasize the view of the parenchymal vessels and to allow a scan angle with respect to the artery below 45° as guided on the basis of the color-Doppler encoding. The PW-Doppler spectral signal was captured from the parenchymal arteries, with the best signal magnification more distal to the pre-hilar artery until the interlobaris, the latter within the intramedullary portion, however far from the flow dividers. The average time needed for carrying out a full investigation at the pre-hilar renal artery and parenchymal sites was 32 ± 13 min, whereas the investigation limited at the parenchymal arteries required 14 ± 6 min.

Calculation of Doppler velocimetric indices

PI, RI, ACC_{sys}, and AT were derived from the analysis of the Doppler spectra and calculated as follows:

$$PI = \frac{(PSV-EDV)}{V_{mean}}, \quad RI = \frac{(PSV-EDV)}{PSV}, \quad ACC_{sys} = \frac{\Delta V_{sys}}{AT}$$

where PSV, EDV, and V_{mean} are the peak systolic, end diastolic, and cycle average velocities, respectively, and ΔV_{sys} and AT (ms) are the velocity gradient and time delay from the beginning to the peak of the systolic phase, respectively (Figure 1a). However, in comparison with a typical normal cycle, characterized by a relatively constant acceleration and an early systolic peak, there are spectra still belonging to the normal hemodynamic pattern, in which the acceleration phase has a double peak or a shoulder that divides the early steeper acceleration from the late less steep phase resulting in slowed systole (Figure 1b).[19] As a result, if the latter waveform patterns are sampled from normal renal arteries, an overestimation of AT and an underestimation of ACC_{sys} may occur and lead to a false diagnosis of RAS (Figure 1c). The new index ACC_{max} (m/s^2) was defined as the mean slope of the systolic acceleration until any significant change of its first derivative in the second half of the acceleration, that is, at the point of the acceleration curve where a slope change is clearly evident (Figure 1d), whereas the maximal acceleration index (AI_{max}, s^{-1}), that is, the maximal slope of the systolic acceleration corrected for the relative district flow regimen (as stated by PSV), was calculated as follows:

$$AI_{max} = \frac{ACC_{max}(m/s^2)}{PSV(m/s)}$$

Statistical analysis

Site distribution, etiology, and degree of RAS were compared by χ^2 analysis. The clusters of each parameter divided on the basis of degree, type, or site of the stenosis were compared by analysis of variance.

According to the aim of the study, based on the evaluation of echo-Doppler velocimetry as a screening test for significant RAS, the sensitivity, specificity as well as the PPV and NPV were calculated for each index; moreover, the ideal cutoff limit was established with the ROC (receiver operating characteristic) curve technique.

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Appendix 1

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