Original Article

Relationship between wave reflection and renal damage in hypertensive patients: a retrospective analysis

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AQ1 **Objective:** Arterial stiffening has harmful effects; peripheral pulse wave reflections deleteriously increase central pressure, but on the contrary they could also possibly be protective, as the pulse is transmitted to the microcirculation to a lesser extent. The aim of this study was, therefore, to explore the relationship between wave reflection and small vessel damage in the kidney.

AQ2 **Methods:** In 216 hypertensive patients, data on renal resistive index, obtained by Doppler ultrasound sampling of the interlobar arteries, as well as augmentation index (AIx) and carotid-to-femoral pulse wave velocity (PWV), were retrospectively analyzed. Reflection magnitude was computed through a triangular flow estimate.

Results: AIx and reflection magnitude were positively correlated with resistive index; age, BMI, central pulse pressure, and cholesterol, but not AIx or reflection magnitude, were predictors of resistive index in

AQ3 multivariate analyses. ~~Crossing tertiles of PWV and AIx, resistive index did not differ between patients with high AIx and low PWV ($n = 25$; 0.632 ± 0.064) and those with low AIx and high PWV ($n = 17$; 0.645 ± 0.053), despite a difference in reflection magnitude (74.9 ± 6.7 vs. $51.2 \pm 7.3\%$; $P < 0.001$).~~

Conclusion: Pressure wave reflection is positively correlated with resistive index in a hypertensive population. No negative relationship was found even adjusting for confounders or when it was examined separately from the influence of arterial stiffness. These findings do not support the hypothesis of peripheral wave reflections having a significant protective role for the microcirculation of a low resistance vascular bed such as the kidney.

Keywords: arterial, arteries, hypertension, kidney, pulse, renal artery

Abbreviations: AIx, Augmentation index; BP, Blood pressure; cDBP, Central diastolic blood pressure; cPP, Central pulse pressure; cSBP, Central systolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; PWV, Pulse wave velocity; RAR, Renal-aorta ratio; UACR, Urinary albumin-to-creatinine ratio

INTRODUCTION

Stiffening of large arteries occurs with aging and is accelerated by cardiovascular risk factors [1]. It reduces the buffering capacity of the arterial tree; thus, peripheral circulation and small vessels are subject to increased flow and pressure pulsatility [2,3]. Increased arterial stiffness, whose gold standard measurement is carotid-to-femoral pulse wave velocity (PWV), has proven to be an independent predictor of cardiovascular events [4], being included among indexes of hypertensive target organ damage in the 2007 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines [5]. Arterial stiffening is also associated with microvascular dysfunction [6] and with heart [7], brain [8–10], and renal [11,12] damage. Furthermore, it has been shown that high pulse pressure (particularly at the central level), whose arterial stiffness is a major determinant, is associated with brain [9] and renal [13–15] damage.

The pulse wave generated by the heart contraction travels along the vessels – at a speed proportional to their stiffness – and it is partially reflected whenever it finds a discontinuity in the arterial tree (branching, tapering, changes in wall structure), generating backward waves. These travel in the opposite direction and add up to the forward wave, further increasing central pulse pressure and cardiac afterload [16]. The augmentation due to the summation of the reflected wave in the ascending aorta can be expressed as a percentage of the resulting pulse pressure, and named augmentation index (AIx); this is a composite index, influenced by the height, phase, and speed of the waves. It has demonstrated too to be a predictor of adverse events, even if the evidence is not as strong and numerous as those for PWV [17].

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Wave reflections in the periphery, however, could also possibly be protective for the microcirculation, as for a basic physical principle, the more a wave is reflected, the less it is transmitted. This phenomenon could be beneficial, especially for organs such as the brain and the kidney, which are characterized by torrential flow and very low resistances [2,3], thus with lower defense against large, and possibly deleterious, oscillations in pressure with the cardiac cycle. The hypothesis, however, has never been proven, neither it has been extensively investigated. Therefore, the aim of the study was to explore the relationship between pulse wave reflection and small vessel damage in the kidney. For this purpose, we assessed the renal resistive index, a known marker of renal vessel damage in hypertensive patients, associated with subclinical impairment in other organs [18–21], and, second, renal function by the estimated glomerular filtration rate (eGFR) and microalbuminuria.

METHODS

Study population

In the present retrospective analysis, we searched our databases (2007–2010) for hypertensive patients who underwent both tonometric measurements and renal Doppler ultrasound in the same morning. These measurements were obtained within 2 h apart. Inclusion criteria were as follows: age at least 18 years; arterial hypertension, defined as blood pressure (BP) at least 140/90 mmHg in two previous separate occasions; or current antihypertensive treatment. Exclusion criteria were as follows: primary kidney disease; presence of only one kidney; eGFR less than 30 ml/min/1.73 m^2; hemodynamically significant stenosis of the main renal artery (renal-aortic ratio, RAR, $\geq$3.5); resistive index differing more than 0.5 or 20% between the two kidneys to avoid patients with unilateral diseases.

The study was conducted according to the principles of the Declaration of Helsinki and in accordance with local guidelines. It was approved by the institutional review committee and all patients gave informed consent for the procedures and the treatment of their clinical data for research purposes.

Blood samples

A blood sample was taken from every patient; tests recommended in the ESH/ESC hypertension guidelines were performed, notably serum lipids, plasma glucose, and serum creatinine; eGFR was calculated with the four-variable MDRD Eq. [22]. Urinary albumin excretion was evaluated as urinary albumin-to-creatinine ratio (UACR) in a single sample collected on the same morning.

Blood pressure measurement

BP was measured at the left arm with an oscillometric device (Omron IT-750; Omron Healthcare, Tokyo, Japan) after 10 min of rest in the supine position; two measurements were taken, and, if they differed more than 5 mmHg, a third one was performed. BP was considered as the average of the last two measurements.

Arterial tonometry

Pulse wave analysis was performed with the SphygmoCor device (AtCor Medical, Sydney, Australia). The radial waveform was acquired through applanation tonometry and the central pressure waveform was obtained through a validated transfer function [23]. This allows the calculation of the central systolic, diastolic, and pulse pressures (cSBP, cDBP, and cPP). AIx is the relative contribution to the increase in central pressure due to the arrival of the reflected wave, and it is expressed as a percentage of the cPP.

PWV was measured with the same device. Briefly, the pulse was recorded sequentially on the carotid and femoral arteries with simultaneous ECG recordings. Time delay was calculated between the feet of the two waves, using the ECG as a reference. Distances were measured on the skin surface with a tape meter and the travel distance of the pulse wave was estimated as (sternal notch to femoral) – (sternal notch to carotid). PWV was calculated as distance/time, and expressed in meter per second [24]. Two measurements were taken and then averaged.

Reflection magnitude

Separation of a pressure waveform into a forward and a backward wave requires simultaneous measurement of flow. However, a mathematical model based on a triangular flow estimate has been proposed and validated, with the start at the time of the initial upstroke, the peak at the first inflection point, and the end at the dicrotic notch of the aortic pressure wave, respectively. For our purposes, no actual absolute value of flow was required in this model [25].

Reflection magnitude was computed as the ratio of the backward pressure amplitude (Pb) to the forward pressure amplitude (Pf). Forward and backward components of the wave are determined quantitatively using the following equations:

$Pf(t) = [Pm(t) + Zc\ F(t)]/2$ and $Pb(t) = [Pm(t) - Zc\ F(t)]/2$,

where Pm(t) is the measured pressure wave, F(t) the estimated triangular flow wave, and Zc the aortic characteristic impedance calculated from averaged value of the 4th to 7th harmonic of the input impedance modulus.

Renal Doppler ultrasound

Scans were performed by an ultrasound device (MyLab 25; Esaote, Florence, Italy) equipped with a high resolution multifrequency convex probe (2.5–4.5 MHz) to assess the renal resistive index, sampling the flow in the interlobar arteries adjacent to medullary pyramids, with a translumbar or anterior approach. Resistive index is defined as (peak systolic velocity – end diastolic velocity)/peak systolic velocity. Three measurements were taken in each kidney and then averaged. For this study, the average of right and left resistive index values was considered.

Statistical analysis

Variables are expressed as mean (standard deviation), except for triglycerides and UACR, expressed as median [25–75%]. Triglycerides have been log-transformed, obtaining a normal distribution, before subsequent analyses. For AIx and PWV, participants were also stratified according to

tertiles of each variable. Pearson's coefficient was used to express linear correlation between variables, except for UACR, in which Spearman's rank correlation was used. Multivariate analyses were performed to evaluate the effect of possible confounders, with the calculation of standardized β for each parameter. Differences between two groups were evaluated with Student's *t*-test (two-tailed, unpaired), or Mann–Whitney *U*-test for UACR. A $P<0.05$ was deemed significant.

RESULTS

The analysis was performed in 216 patients. They were predominantly men, and most of them were on pharmacological therapy (Table 1); 39% of treated patients were receiving AT1-receptor blockers, 35% angiotensin-converting enzyme (ACE) inhibitors, 33% diuretics, 23% calcium channel blockers, 13% β-blockers, and 4% α-1-blockers.

PWV, AIx, and reflection magnitude were all positively correlated with resistive index (Fig. 1). These relationships retained their significance in two-variable multivariate models such as PWV + AIx ($\beta=0.392$ and 0.245, respectively, $P<0.001$ for both, adjusted $R^2=0.244$) or PWV + reflection magnitude ($\beta=0.408$ and 0.229, $P<0.001$ for both, $R^2=0.238$); the correlation of PWV was independent of cPP (PWV + cPP: $\beta=0.207$ and 0.503, $P=0.001$ and <0.001, $R^2=0.386$), whereas those of AIx and reflection magnitude were not (AIx + cPP: $\beta=0.022$ and 0.587, $P=0.726$ and <0.001, $R^2=0.353$; reflection magnitude + cPP: $\beta=0.011$ and 0.594, $P=0.862$ and <0.001, $R^2=0.352$).

The positive univariate correlations were present in both treated and untreated patients (see Figure, Supplemental Digital Content n. 1, http://links.lww.com/HJH/A277, showing plots and regression lines).

Table 2 shows other univariate correlations of resistive index, AIx, and reflection magnitude. Variables most strongly associated with resistive index are pulse pressure (particularly central), age, and PWV. eGFR was correlated with PWV ($R=-0.282$, $P<0.001$) and resistive index ($R=-0.306$, $P<0.001$), but not with AIx or reflection magnitude ($P=$ not significant). UACR was not correlated with PWV, AIx, reflection magnitude, or resistive index ($P=$ not significant).

PWV, heart rate, mean BP, height, and sex are determinants of AIx. When all these confounders were entered together in a multivariate model, AIx maintained a significant positive, though weaker, relationship with resistive index ($\beta=0.167$; $P=0.044$).

When all variables with a significant correlation with resistive index at the univariate analysis were entered in the multivariate model, only age, BMI, cDBP, cPP, and cholesterol were independent predictors of resistive index, without any significant correlation of AIx or reflection magnitude (Table 3, model 1 and 2, respectively). In both models, the relationship between PWV and resistive index was of borderline significance (Table 3). Similar results were obtained applying the models separately in treated and untreated participants: there was no significant correlation between AIx, or reflection magnitude, and resistive index (all $P=$ not significant).

To overcome the influence of PWV on AIx, patients were divided in tertiles and the two categorizations were crossed.

TABLE 1. Clinical characteristics and vascular measurements

	Overall	Untreated	Treated	*P* U vs. T
	n = 216 (100%)	*n* = 126 (58%)	*n* = 90 (42%)	
Sex, M/F, %	136/80 (63/37)	56/34 (62/38)	80/46 (63/37)	0.89
Age, years	53.3 (11.7)	49.7 (10.7)	55.8 (11.2)	<0.001
Height, cm	170.5 (8.8)	171.1 (9.5)	170.2 (8.3)	0.50
BMI, kg/m^2	27.3 (4.2)	26.7 (4.5)	27.8 (3.9)	0.049
Total cholesterol, mmol/l	5.32 (1.03)	5.30 (1.09)	5.33 (0.99)	0.87
LDL cholesterol, mmol/l	3.26 (0.90)	3.21 (1.03)	3.28 (0.85)	0.60
HDL cholesterol, mmol/l	1.31 (0.38)	1.39 (0.44)	1.26 (0.32)	0.042
Triglycerides, mmol/l	1.41 [0.96–1.96]	1.46 [0.89–1.94]	1.37 [0.99–1.99]	0.36
Blood glucose, mmol/l	5.21 (0.95)	5.16 (0.86)	5.25 (1.01)	0.51
bSBP, mmHg	144.6 (16.9)	146.7 (14.0)	143.1 (18.6)	0.10
bDBP, mmHg	85.0 (10.4)	88.0 (9.7)	82.9 (10.5)	<0.001
bPP, mmHg	59.5 (14.5)	58.7 (12.1)	60.1 (16.0)	0.46
cSBP, mmHg	133.6 (16.9)	135.7 (14.2)	132.1 (18.5)	0.10
cDBP, mmHg	86.3 (10.6)	89.4 (9.7)	84.1 (10.7)	<0.001
cPP, mmHg	47.4 (14.0)	46.4 (11.5)	48.1 (15.5)	0.37
Mean BP, mmHg	106.7 (12.0)	110.0 (10.6)	104.4 (12.4)	<0.001
Heart rate, bpm	66.1 (10.5)	67.4 (10.6)	65.2 (10.3)	0.14
PWV, m/s	8.52 (1.81)	8.20 (1.64)	8.74 (1.91)	0.032
AIx, %	27.5 (11.1)	28.2 (11.6)	27.4 (11.0)	0.63
Reflection magnitude, %	64.2 (12.7)	63.8 (13.0)	64.4 (12.6)	0.75
RI	0.632 (0.066)	0.616 (0.059)	0.643 (0.068)	0.003
Creatinine, mmol/l	83.7 (20.8)	80.4 (15.8)	86.0 (23.4)	0.065
eGFR, ml/min/1.73 m^2	81.7 (17.5)	85.5 (18.5)	79.0 (16.7)	0.015
UACR, mg/mmol	0.6 [0.2–2.1]	0.7 [0.2–1.4]	0.6 [0.2–2.5]	0.79

Data are mean (SD), median [25–75%], or categories and percentages. AIx, augmentation index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PWV, carotid-to-femoral pulse wave velocity; RI, renal resistive index; UACR, urinary albumin-to-creatinine ratio.

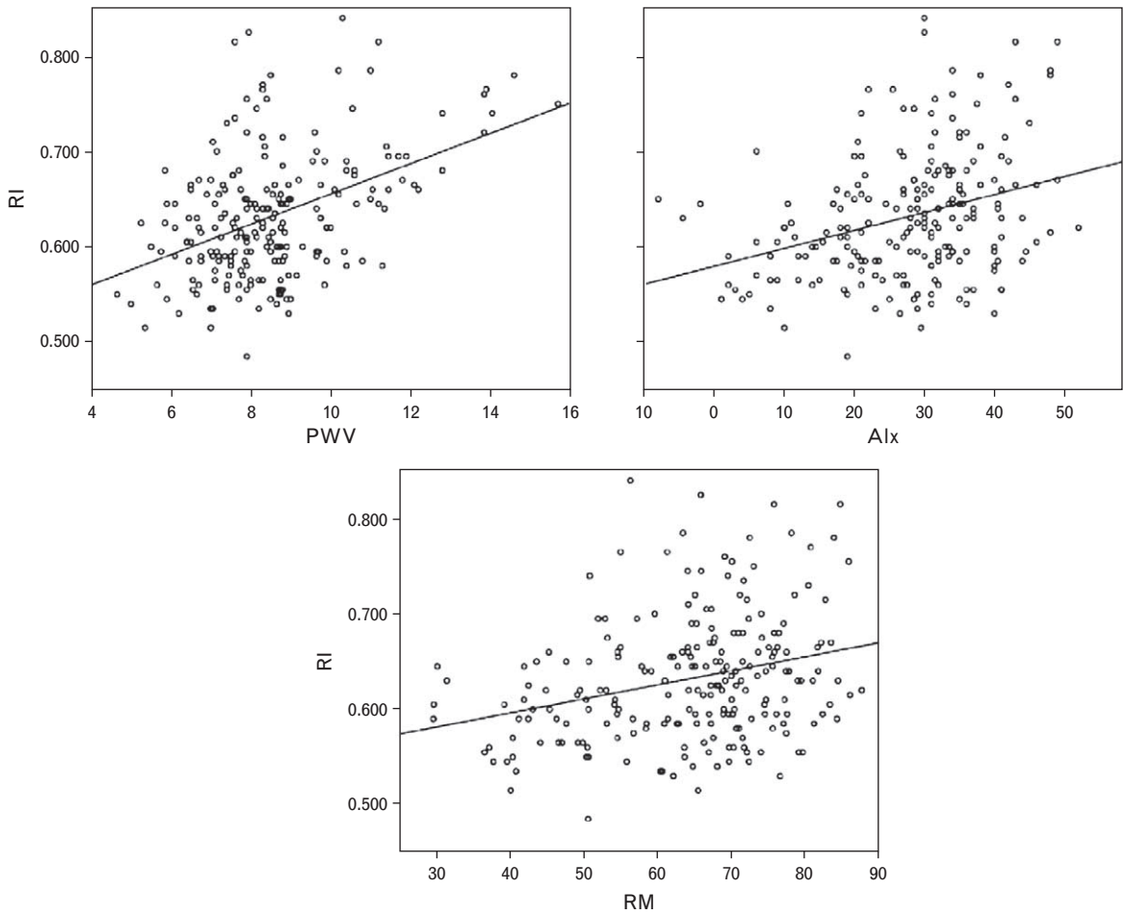

FIGURE 1 Linear correlations of renal resistive index with carotid-to-femoral pulse wave velocity (PWV, top left: R 0.440, $P<0.0001$), augmentation index (AIx, top right: R 0.322, $P<0.0001$), and reflection magnitude (bottom: R 0.285, $P<0.001$). RM, reflection magnitude.

TABLE 2. Univariate correlations for renal resistive index, augmentation index, and reflection magnitude

	RI	AIx	RM
Sex (β female vs. male)	0.291	0.402	0.312
Age	0.589	0.427	0.356
Height	−0.267	−0.428	−0.296
BMI	0.145	−0.150	0.161
Brachial SBP	0.244	0.209	0.165
Brachial DBP	−0.352	–	–
Brachial pulse pressure	0.538	0.182	0.139
Central SBP	0.270	0.467	0.415
Central DBP	−0.358	–	–
Central pulse pressure	0.599	0.511	0.463
Mean blood pressure	–	0.277	0.222
Heart rate	−0.224	−0.434	−0.578
Carotid-to-femoral pulse wave velocity	0.440	0.196	0.139
AIx	0.322		0.879
RM	0.285	0.879	
Serum creatinine	–	−0.190	−0.174
Estimated GFR	−0.306	–	–
Total cholesterol	0.223	0.170	0.151
LDL cholesterol	0.203	0.150	–
HDL cholesterol	–	0.378	0.274
Blood glucose	–	−0.164	–
Antihypertensive therapy (β yes vs. no)	0.198	–	–

R is shown for $P<0.05$ only. AIx, augmentation index; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RM, reflection magnitude.

TABLE 3. Multivariate models for renal resistive index

	Model 1 with AIx		Model 2 with reflection magnitude	
	β	*P*	β	*P*
Sex (female vs. male)	0.133	0.070	0.132	0.078
Age	**0.196**	0.013	**0.205**	0.009
Height	0.090	0.232	0.089	0.225
BMI	**0.162**	0.002	**0.156**	0.003
Central DBP	**−0.240**	0.000	**−0.238**	0.000
Central pulse pressure	**0.376**	0.000	**0.381**	0.000
Heart rate	−0.061	0.316	−0.065	0.328
eGFR	−0.094	0.082	−0.091	0.093
Carotid-to-femoral pulse wave velocity	0.127	0.056	0.132	0.051
AIx	−0.007	0.928		
Reflection magnitude			−0.028	0.709
Total cholesterol	**0.115**	0.026	**0.113**	0.029
Antihypertensive therapy (yes vs. no)	−0.015	0.789	−0.027	0.622
Adjusted R^2	**0.571**		**0.572**	

R values in bold stand for $P<0.05$. AIx, augmentation index; GFR, glomerular filtration rate.

AQ10

No significant difference in resistive index was observed between patients with high AIx and low PWV and those with low AIx and high PWV ($n=25$ vs. 17; 0.632 ± 0.064 vs. 0.645 ± 0.053; $P=0.9$; Fig. 2). No significant difference was found also comparing eGFR (82.7 ± 16.2 vs. 76.8 ± 12.0 ml/min/1.73 m^2, $P=0.24$) or UACR [5 (0–10) vs. 6 (2–107) mg/g, $P=0.42$). Patients with high AIx and low PWV showed higher reflection magnitude compared with those with low AIx and high PWV (74.9 ± 6.7 vs. 51.2 ± 7.3%; $P<0.001$).

Results did not change when analyzed in untreated and treated hypertensive patients (see Table, Supplemental Digital Content n. 2, http://links.lww.com/HJH/A278).

DISCUSSION

It has been speculated that peripheral wave reflection could be protective, reducing the transmission of pulsatility to the microcirculation, particularly in organs with low resistances to flow [2,3]. In the present study, we explored the putative protective role of wave reflections on renal small vessels by testing the hypothesis that a higher wave reflection, corresponding to a lower transmission, would be associated with a lower vascular damage, measured as renal resistive index.

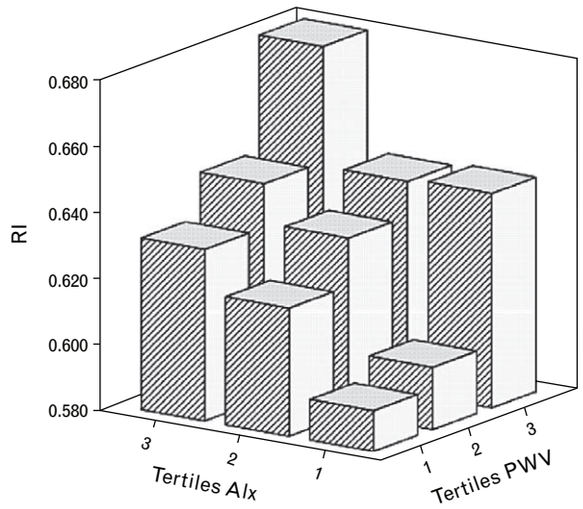

FIGURE 2 Renal resistive index across tertiles of carotid-to-femoral pulse wave velocity (PWV) and augmentation index (AIx).

The main result of this study is that AIx, an estimate of wave reflection [24], has a positive, rather than the hypothesized negative, correlation with resistive index. However, AIx is an approximate marker of the reflection magnitude, as it is a measurement of the superimposition of the backward wave on the forward pressure wave, and thus influenced not only by the degree of reflection, but also by the time the pulse wave travels forth and back. The latter depends on speed, that is, PWV – in its turn influenced by the distending pressure – and on distance, which is correlated to body length, that is, height. Indeed, PWV, heart rate, mean BP, height, and sex are confirmed determinants of AIx in our hypertensive population [26–28]. Nevertheless, when confounders were introduced in the model, still a positive correlation between AIx and resistive index was found. Furthermore, AIx failed to show a negative correlation with resistive index also when tested in a model together with other determinants of resistive index.

As expected, the main indexes acquired through tonometry, AIx and PWV, were correlated [24]. To overcome this confounding effect, we divided the hypertensive population into tertiles and crossed the two categorizations. Patients with a high AIx despite a low PWV were considered having high reflection, and those with a low AIx despite a high PWV as having low reflection. Noteworthy, no difference in markers of renal damage, including not only resistive index but also eGFR and UACR, was observed between the low-reflection and high-reflection groups.

The computation of the reflection magnitude [25] represented another approach overcoming the problem of the interaction between AIx and PWV. The analysis of reflection magnitude confirms a positive correlation between wave reflection and renal resistances, also

confirming that patients with high AIx/low PWV do have higher reflections than those with low AIx/high PWV.

Our findings are in contrast with preliminary data from McDonnell [29] showing an inverse relation between retinal resistive index and AIx in 67 participants ($r = -0.26$, $P = 0.047$) along with a significantly lower resistive index in high AIx/low PWV than in low AIx/high PWV. Discrepancy with our results is likely explained by the different clinical characteristic of the enrolled population, which was plausibly normotensive. An alternative explanation could reside in the difference in arterial districts studied.

Another aspect of our findings is that the positive relationship between wave reflection and resistive index, observed in the univariate analysis, disappeared in a model comprising PWV and other confounders, whereas resistive index tended to be related to PWV, an index of arterial stiffness. This suggests that large artery stiffness is definitely deleterious for renal microvasculature, in agreement with previous results showing correlation between PWV and resistive index [30,31]. Furthermore, studies investigating the role of pulsatile hemodynamics in cardiovascular morbidity/mortality [32,33] demonstrated that forward and backward wave amplitudes (critically influenced by arterial stiffness) were associated with negative outcomes, while the association between reflection indexes and mortality was weaker. Taken together, these observations suggest that the positive relationship between AIx and resistive index could be mainly determined by the deleterious effects of aortic stiffness on both renal hemodynamics and wave reflection.

Some limitations should be acknowledged. First, indexes here chosen could lack the necessary sensitivity and/or specificity to properly test the original hypothesis. We already pointed out the composite nature of AIx, but it has to be noticed that it bears a very strong correlation with the actual reflection magnitude, and that the expedient of crossing it with PWV did indeed succeed in finding subgroups with high and low reflection. ~~On the other hand,~~ the model for wave separation uses a crude approximation of flow, even if it results in a good agreement with actual measurements and it has proven to have a clinical value [32].

The role of resistive index as a marker of renal vascular damage has also been questioned, as it depends not only upon renal vascular resistances but also upon other factors, such as large artery pulsatility and central BP [30,34]. Nevertheless, it is accepted that renal resistive index, though measured at the level of the interlobar arteries, is an index of downstream renal microvascular impedance [35], and prospectively correlated with renal prognosis [36,37]. Furthermore, similar results were obtained when eGFR or UACR, established markers of hypertensive renal damage [5], were considered instead of resistive index.

Tonometry and resistive index measurements were not measured contemporaneously, although within 2 h apart and in similar conditions. BP changes in time, but, given their strong correlation with resistive index values, central BP values analyzed here appear a reasonable estimate of central hemodynamics. Furthermore, AIx and reflection magnitude estimated wave reflection in the ascending aorta, which could be different from that reaching the renal circulation. The kidney itself with its low resistances produces little wave reflection, while we evaluated the global sum of reflections from the whole body.

Finally, this study was performed in a hypertension referral center with patients not selected on a random basis; thus, they could not be representative of the general hypertensive population or of populations with different cardiovascular risk.

In conclusion, pressure wave reflection, estimated through AIx, is positively correlated with resistive index in a hypertensive population. No negative correlation was found even when confounders were added and when it was examined separately from the influence of arterial stiffness. Also the reflection magnitude, computed as the ratio between the backward and forward wave amplitudes, is positively associated with resistive index. These findings, although limited by the cross-sectional design of the study, do not support the hypothesis of peripheral wave reflection having a significant protective role for the microcirculation of a low resistance vascular bed such as that of the kidney. Further prospective longitudinal studies are needed to investigate the cross-talk between the microcirculation and macrocirculation and the pathophysiological role of wave reflections, especially in conditions of high cardiovascular risk such as arterial hypertension.

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Conflicts of interest

~~None declared.~~

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Reviewers' Summary Evaluations

Reviewer 1

The strength of the study is in its design and in the use of sophisticated methodology.

The weakness is that study subjects were receiving various antihypertensive agents which might have had diverse hemodynamic effects. Furthermore while important to experts in wave dynamics, the topic investigated may be of lesser interest to those more broadly interested in the management of hypertension.

Reviewer 2

Renal resistive index is not an adequate marker of renal vascular damage. This measure not only depends on renal vascular resistance but also upon other factors. The same is true for eGFR. Unfortunately, the authors did not determine renal blood flow which would have enabled them to calculate renal vascular resistance.

HJH

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During the preparation of your manuscript for typesetting, some queries have arisen. These are listed below. Please check your typeset proof carefully and mark any corrections in the margin as neatly as possible or compile them as a separate list. This form should then be returned with your marked proof/list of corrections to the Production Editor.

QUERIES: to be answered by AUTHOR/EDITOR

QUERY NO.	QUERY DETAILS	RESPONSE
<AQ1>	Please check whether the intended meaning of the following sentence is retained after making the edits. "'Arterial stiffening has harmful effects; peripheral pulse wave reflections deleteriously increase central pressure, but on the contrary they could also possibly be protective, as the pulse is transmitted to the microcirculation to a lesser extent'.	
<AQ2>	Please check whether the intended meaning of the following sentence is retained after making the edits. "'In 216 hypertensive patients, data on renal resistive index, obtained by Doppler ultrasound sampling of the interlobar arteries, as well as augmentation index (AIx) and carotid to femoral pulse wave velocity (PWV), were retrospectively analyzed".	
<AQ3>	The intended meaning of the following sentence is not clear. Please check. "'Crossing tertiles of PWV and AIx, resistive index did not differ between patients with high AIx and low PWV (n = 25; 0.632 ± 0.064) and those with low AIx and high PWV (n = 17; 0.645 ± 0.053), despite a difference in reflection magnitude (74.9 ± 6.7 vs. 51.2 ± 7.3%; P <0.001)'.	
<AQ4>	Please provide the expanded form of MDRD Eq.	
<AQ5>	The following sentence seems to be incomplete without the term "on the one hand". Please provide the alternative for	

	the same. “On the other hand … and it has proven to have a clinical value”.
<AQ6>	As per the style of the journal, the article should have a mention of the ‘Conflicts of interest’ in a separate section under Acknowledgement(s) section. Please update the COI from 'None declared' to 'There are no conflicts of interest' if you have no conflict of interest or please provide an appropriate statement for the same.
<AQ7>	Please check the author names in Ref.[16].
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<AQ9>	Please provide the volume number and page range in Ref.[33].
<AQ10>	Tables 1–3 have been slightly reformatted. Please check.